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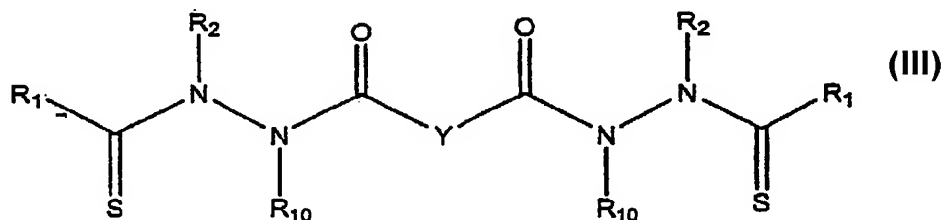
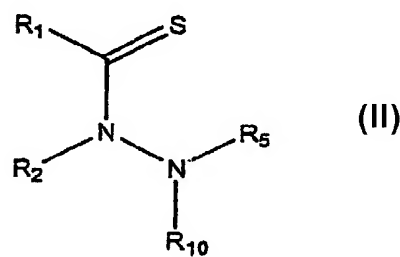
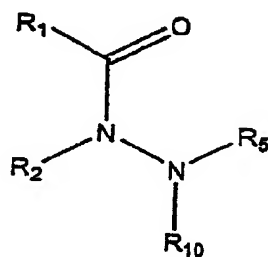
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[Continued on next page]

(54) Title: SYNTHESIS OF TAXOL ENHANCERS



(57) Abstract: Disclosed is a method of preparing a thiohydrazide compound a formula (II) from a hydrazide starting compound of formula (I). The method comprises reacting the starting compound of formula (I) with a thionylating reagent. The thiohydrazide of formula (II) can be reacted with compounds of the formula Z-C(O)-Y-C(O)-z or HO-C(O)-Y-C(O)-OH and a carboxylic acid activating agent to produce compound of formula III which enhance the anti-cancer activity of taxol and analogs thereof. The variables R1, R2, R5, R10, Y and Z are as defined in the claims.





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SYNTHESIS OF TAXOL ENHANCERS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/304,318, filed July 10, 2001, the entire teachings of which are incorporated
5 herein by reference.

BACKGROUND OF THE INVENTION

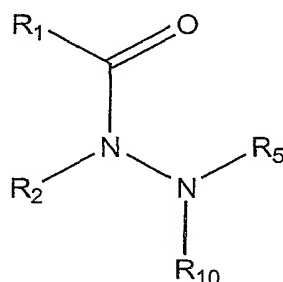
Many new drugs are now available to be used by oncologists in treating patients with cancer. Often, tumors are more responsive to treatment when anti-cancer drugs are administered in combination to the patient than when the same
10 drugs are administered individually and sequentially. One advantage of this approach is that the anti-cancer agents often act synergistically because the tumors cells are attacked simultaneously with agents having multiple modes of action. Thus, it is often possible to achieve more rapid reductions in tumor size by administering these drugs in combination. Another advantage of combination chemotherapy is that
15 tumors are more likely to be eradicated completely and are less likely to develop resistance to the anti-cancer drugs being used to treat the patient.

One serious limitation of combination chemotherapy is that anti-cancer agents generally have severe side effects, even when administered individually. For example, the well known anti-cancer agent taxol causes neutropenia, neuropathy,
20 mucositis, anemia, thrombocytopenia, bradycardia, diarrhea and nausea. Unfortunately, the toxicity of anti-cancer agents is generally additive when the drugs are administered in combination. As result, certain types of anti-cancer drugs are generally not combined. The combined toxic side-effects of those anti-cancer drugs that are administered simultaneously can place severe limitations on the quantities
25 that can be used in combination. Often, it is not possible to use enough of the combination therapy to achieve the desired synergistic effects. Therefore, there is an urgent need for agents which can enhance the desirable tumor attacking properties of anti-cancer agents without further increasing their undesirable side-effects, and methods for synthesizing such agents.

SUMMARY OF THE INVENTION

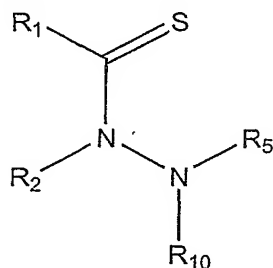
It has been reported in the co-pending US Provisional Applications entitled TAXOL ENHANCER COMPOUNDS, filed July 10, 2001, (Application No. 60/304,252), TAXOL ENHANCER COMPOUNDS, filed March 6, 2002 (Application No. 60/361,946) and TAXOL ENHANCER COMPOUNDS, filed March 6, 2002 (Application No. 60/361,936) that certain bis[thio-hydrazide amide] compounds significantly enhance the anti-cancer activity of taxol and analogs of taxol. The entire teachings of these applications are incorporated herein by reference. Disclosed herein are methods of preparing these taxol enhancing compounds.

- 10 One embodiment of the present invention is a method of preparing a thiohydrazide product compound from a hydrazide starting compound. The hydrazide starting compound is represented by Structural Formula (I):



(I).

- 15 The thiohydrazide product compound is represented by Structural Formula (II):

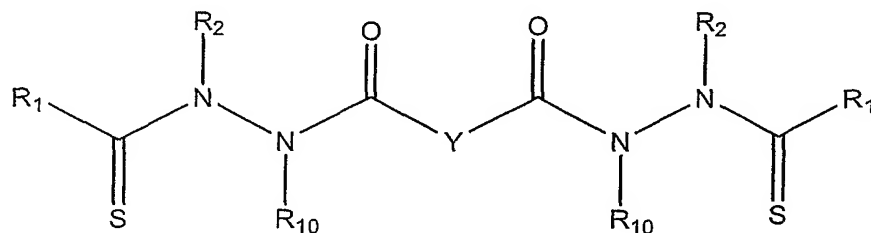


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(II).

In Structural Formulas (I)-(II), R_1 and R_2 are independently an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group, or R_1 and R_2 , taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring. When R_2 is an aryl group or a substituted aryl group, then R_5 is a hydrazine protecting group; and when R_2 is an aliphatic or substituted aliphatic group, then R_5 is -H or a hydrazine protecting group. R_{10} is -H or a substituted or unsubstituted alkyl group (preferably -H or an unsubstituted alkyl group, more preferably -H or methyl). The method comprises the step of reacting the starting compound with a thionylating reagent.

Another embodiment of the present invention is a method of preparing a product compound represented by Structural Formula (III):



(III).

The method comprises the step of reacting $Z-C(O)-Y-(CO)-Z$ or $HO-C(O)-Y-(CO)-OH$ and a carboxylic acid activating agent with the thiohydrazide represented by Structural Formula (II), wherein R_5 is -H.

R_1 , R_2 and R_{10} in Structural Formula (III) are as described for Structural Formulas (I)-(II).

Y is a covalent bond or a substituted or unsubstituted straight chained hydrocarbonyl group. Preferably, Y is a covalent bond, $-C(R_7R_8)-$, $-CH_2CH_2-$, *trans*-($CH=CH$)-, *cis*-($CH=CH$)-, $-(CC)-$ or a 1,4-phenylene group. More preferably, Y is a covalent bond or $-C(R_7R_8)-$.

R_7 and R_8 are each independently -H, an aliphatic or substituted aliphatic group, or R_7 is -H and R_8 is a substituted or unsubstituted aryl group, or, R_7 and R_8 , taken together, are a C2-C6 substituted or unsubstituted alkylene group.

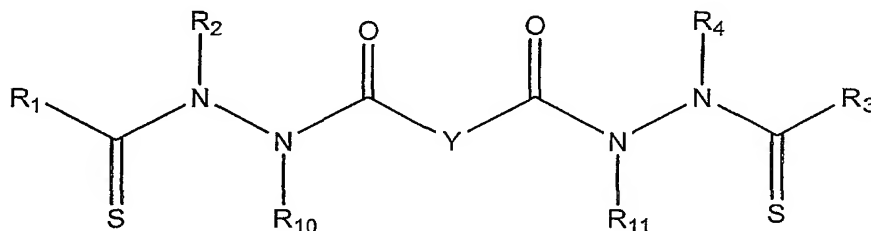
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Each Z is a leaving group.

Another embodiment of the present invention is a method of preparing a product compound represented by Structural Formula (III) from a hydrazide starting compound represented by Structural Formula (I). The hydrazide starting compound is thionylated to form a thiohydrazide represented by Structural Formula (II), as described above. If R_5 is -H, then $Z-C(O)-Y-(CO)-Z$ or $HO-C(O)-Y-(CO)-OH$ and a carboxylic acid activating agent is reacted with the thiohydrazide represented by Structural Formula (II) to form the product compound represented by Structural Formula (III), as described above. If R_5 is a hydrazine protecting group, the hydrazine protecting group is first removed before reacting with $Z-C(O)-Y-(CO)-Z$. Z and Y are as described above.

DETAILED DESCRIPTION OF THE INVENTION

The methods disclosed herein can also be used to prepare bis[thio-hydrazide amide] compounds, which, as the term is used herein, refers to a compound represented by Structural Formula (I). In addition, asymmetrical bis[thio-hydrazide amide] compounds can also be prepared by suitable modifications of these procedures. The term "asymmetrical bis[thio-hydrazide amide] compound" refers to a compound represented by Structural Formula (IV):



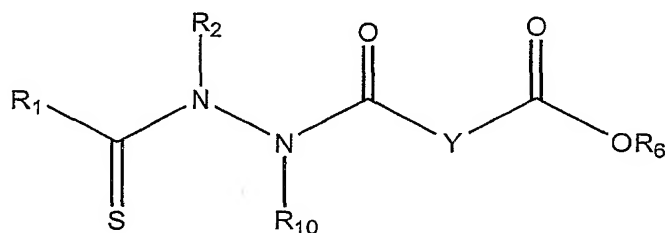
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(IV).

R_1 , R_2 , R_7 , R_8 , R_{10} , and Y are as defined above. R_3 and R_4 are independently an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group, or R_3 and R_4 , taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic

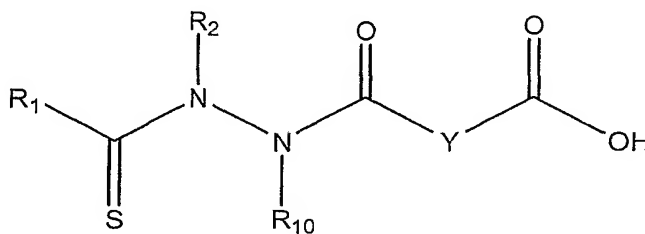
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ring. R_3 and R_4 are independently selected from R_1 and R_2 . R_{11} is -H or a substituted or unsubstituted alkyl group and is selected independently of R_8 . The method comprises a first step in which a compound represented by HOOC-Y-COOR_6 is amidated with a first thiohydrazide starting material represented by Structural Formula (II). R_6 is a carboxylic acid protecting group. The amidation forms a first intermediate represented by Structural Formula (V):



(V).

The protecting group is then removed from the carboxylic acid to form a second intermediate with a free carboxylic acid group. The second intermediate is represented by Structural Formula (VI):



(VI).

The second intermediate is then amidated with a second thiohydrazide starting material represented by Structural Formula (II). The second thiohydrazide starting compound is typically different from the first thiohydrazide starting compound, thereby forming the asymmetrical bis[thiohydrazide-amide] represented by Structural Formula (IV).

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R₁ in Structural Formulas (I)-(VI) can be a substituted or unsubstituted aryl group (preferably a substituted or unsubstituted phenyl group). When R₁ in Structural Formulas (I)-(VI) is aryl or substituted aryl, R₂ can be a substituted or unsubstituted aliphatic group, preferably a substituted or unsubstituted lower alkyl group (e.g.,
5 methyl, ethyl, *n*-propyl, *n*-butyl or *n*-pentyl). Alternatively, when R₁ in Structural Formula (I)-(VI) is aryl or substituted aryl, R₂ can be a substituted or unsubstituted aryl group, preferably a substituted or unsubstituted phenyl group.

R₁ in Structural Formula (I)-(VI) can also be a substituted or unsubstituted aliphatic group, preferably a substituted or unsubstituted lower alkyl group (e.g.,
10 methyl, ethyl, *n*-propyl, *n*-butyl or *n*-pentyl). When R₁ in Structural Formula (I)-(VI) is a substituted or unsubstituted aliphatic group, R₂ can be a substituted or unsubstituted aryl group, preferably a substituted or unsubstituted phenyl group. Alternatively, when R₁ in Structural Formula (I)-(VI) is a substituted or unsubstituted aliphatic group, R₂ can also be a substituted or unsubstituted aliphatic
15 group, preferably a substituted or unsubstituted lower alkyl group (e.g., methyl, ethyl, *n*-propyl, *n*-butyl or *n*-pentyl).

In another alternative, R₂ in Structural Formulas (I)-(VI) is an aliphatic group or a substituted aliphatic group. When R₂ in Structural Formulas (I)-(VI) is an aliphatic group or a substituted aliphatic group, R₁ is preferably a lower alkyl group
20 or a substituted lower alkyl group.

In yet another alternative, R₂ in Structural Formulas (I)-(VI) is an aryl group or a substituted aryl group, more preferably a phenyl group or a substituted phenyl group.

Preferably in Structural Formulas (I)-(VI), R₁ is a substituted or unsubstituted
25 aryl group, R₂ is methyl or ethyl, R₇ is -H and R₈ is -H or methyl.

“Thionylating agent” is a reagent which, under suitable, conditions, can convert a ketone, ester or amide into a thioketone, thioester or thioamide, respectively. There are many thionylating agents known to one of ordinary skill in the art. Examples include Lawesson’s Reagent, tetraphosphorus pentasulfide,
30 Scheeren’s reagent (P₄S₁₀-Na₂S),

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P_4S_{10} -N(ethyl)₃, Davy' Reagent and Heimgarner' reagent. Also known are conditions suitable for carrying out these conversions with thionylating agents. For example, such conditions are disclosed in Fieser and Fieser, "Reagents for Organic Synthesis", Volume 1, John Wiley & Sons, (1975) page 870-71, Fieser and Fieser, 5 "Reagents for Organic Synthesis", Volume 5, John Wiley & Sons, (1975) page 653 and publications cited therein. Suitable conditions are also described in *Bull. Soc. Chim. Belg.* 87:223, 229, 525 (1978), *Synthesis* 1979:941 (1979), *Tetrahedron* 35:2433 (1979) and *Tetrahedron* 21:4061 (1980). Descriptions of these reagents can also be found in Metzner and Thuillier "Sulfur Reagents in Organic Synthesis", 10 Academic Press, 1994. The relevant portions of these publications are incorporated herein by reference.

Applicants have discovered that thionylating agents can similarly convert hydrazides to the corresponding thiohydrazide. Conditions for thionylating hydrazides are generally the same or similar to those used for thionylating ketones, 15 esters or amides. Although some modification of those conditions may be necessary when reacting hydrazides with thionylating reagents, such modifications can readily be determined by one of ordinary skill in the art. Suitable conditions for preparing thiohydrazides from hydrazides are described in the following paragraphs.

To thionylate hydrazides, typically about one equivalent of the hydrazide is 20 reacted with the thionylating reagent in an inert solvent. In some cases, it may be desirable to use a slight excess of thionylating reagent, for example up to about 1.5 equivalents, preferably no more than about 1.1 equivalents. Suitable inert solvents include ethereal solvents (e.g., diethyl ether, tetrahydrofuran, glyme and 1,4-dioxane), aromatic solvents (e.g., benzene and toluene) or chlorinated solvents (e.g., 25 methylene chloride and 1,2-dichloroethane). The reaction is carried out at temperatures ranging from about room temperature to about 150° C, preferably from about 75° C to about 125° C. Representative conditions for carrying out these reactions are found in Examples 1-9.

The term "amidating a carboxylic acid" refers to converting a carboxylic acid 30 to an amide or a hydrazide. Many methods for converting a carboxylic acid to an amide are known in the art. Applicants have discovered that these methods can be

used to prepare to the bis[thio-hydrazide amide] compounds of the present invention. Typically, the carboxylic acid is first converted into a group that is more readily displaced by an amine or hydrazine than -OH. Thus, -OH is converted into a better leaving group. A "leaving group" is a group which can readily be displaced by
5 a nucleophile.

In one example, -OH of the carboxylic acid is converted into a better leaving group by replacing it with a halogen, typically with chloride. The carboxylic acid is thereby converted into an acid halide, e.g., an acid chloride. Reagents suitable for preparing acid chlorides from carboxylic acids are well known in the art and include
10 thionyl chloride, oxalyl chloride, phosphorus trichloride and phosphorus pentachloride. Typically, each carboxylic acid group is reacted with about one equivalent or a slight excess of thionyl chloride, oxalyl chloride, phosphorus trichloride and phosphorus pentachloride in an inert solvent such as an ethereal solvent (e.g., diethyl ether, tetrahydrofuran or 1,4-dioxane), a halogenated solvent
15 (e.g., methylene chloride or 1,2-dichloroethane) or aromatic solvent (e.g., benzene or toluene). When oxalyl chloride is used, a tertiary amine is often added to accelerate the reaction in quantities ranging from a catalytic amount to about one equivalent relative to oxalyl chloride.

Alternatively, the carboxylic acid is first converted into an "activated ester".
20 An ester -COOR is said to be "activated" when -OR is readily displaced by an amine or hydrazine. -OR is more easily displaced as R becomes more electron withdrawing. Some activated esters are sufficiently stable that they can be isolated, e.g., esters wherein R is phenyl or substituted phenyl. For example, diphenylmalonate can be prepared from malonyl chloride and phenol, both
25 commercially available from Aldrich Chemical Co., Milwaukee, WI., by procedures described above. Other activated esters are more reactive and are generally prepared and used *in situ*.

Formation of an activated ester *in situ* requires a "coupling agent", also referred to as a "carboxylic acid activating agent", which is a reagent that replaces
30 the hydroxyl group of a carboxyl acid with a group which is susceptible to nucleophilic displacement. Examples of coupling agents include 1,1'-

carbonyldiimidazole (CDI), isobutyl chloroformate, dimethylaminopropylethylcarbodiimide (EDC), dicyclohexyl carbodiimide (DCC). When amidating by *in situ* generation of an activated ester, an excess of either the carboxylic acid or hydrazine can be used (typically a 50% excess, more typically about a 10-15% excess).

- 5 However, it is more common when carrying out the present invention to use the hydrazine compound as the limiting reagent. Generally, from about 1.0 equivalent to about 10 equivalents of coupling agent are used relative to each carboxylic acid group, preferably from about 1.0 equivalent to about 1.5 equivalents. When DCC is used, a weak acid such as 1-hydroxybenzotriazole (HOBt) is often added to
- 10 accelerate the reaction. Typically, about between one to about 1.5 equivalents of HOBt relative to DCC is used, preferably between about one to about 1.2 equivalents. The reaction is generally carried out in inert, aprotic solvents, for example, halogenated solvents such as methylene chloride, dichloroethane and chloroform, ethereal solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether
- 15 and dimethylformamide. Suitable reaction temperature generally range from between about 0° to about 100°, but the reaction is preferably carried out at ambient temperature. Representative conditions for carrying out these reactions are found in Examples 1-9.

The compound represented by Structural Formula (V) comprises a carboxylic

20 acid protecting group. Suitable protecting groups for carboxylic acids and conditions for protecting and deprotecting carboxylic acids with these groups are known in the art and are described, for example, in Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (1991). The entire teachings of Greene and Wits are incorporated herein by reference. Specific examples of suitable carboxylic

25 acid protecting groups for Structural Formula (V) include, but are not limited to *tert*-butoxy, benzoxy, phenoxy, diphenylmethoxy, triphenylmethoxy and methoxymethyl.

The compounds represented by Structural Formulas (I) and (II) can comprise a hydrazine protecting group. Amine protecting groups can also be used for

30 protecting hydrazine groups, and conditions which are suitable for protecting and deprotecting amines with these protecting groups are also suitable for use with hydrazines. Protecting groups for amines and conditions for protecting and

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deprotecting amines with these protecting groups are known in the art and are disclosed, for example, in Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (1991). Specific examples of suitable hydrazine protecting groups include, but are not limited to, *tert*-butoxycarbonyl (BOC),
5 benzyloxycarbonyl (CBZ) and fluorenylmethyloxycarbonyl (Fmoc).

A "straight chained hydrocarbonyl group" is an alkylene group, i.e., $-(CH_2)_x-$, with one or more (preferably one) methylene groups is optionally replaced with a linkage group. x is a positive integer (e.g., between 1 and about 10), preferably between 1 and about 6, more preferably between 1 and 2. A "linkage group" refers
10 to a functional group which replaces a methylene in a straight chained hydrocarbonyl. Examples of suitable linkage groups include a ketone ($-C(O)-$), alkene, alkyne, phenylene, ether ($-O-$), thioether ($-S-$), or amine $[-N(R^a)]-$, wherein R^a is defined below. A preferred linkage group is $-C(R_7R_8)-$, wherein R_7 and R_8 are defined above. Suitable substituents for an alkylene group and a hydrocarbonyl group are those
15 which do not substantially interfere with the reactions described herein. R_7 and R_8 are preferred substituents for an alkylene or hydrocarbonyl group.

An aliphatic group is a straight chained, branched or cyclic (non-aromatic hydrocarbon which is completely saturated or which contains one or more units of unsaturation. Typically, a straight chained or branched aliphatic group has from one
20 to about twenty carbon atoms, preferably from one to about ten, and a cyclic aliphatic group has from three to about eight ring carbon atoms. An aliphatic group is preferably a straight chained or branched alkyl group, e.g, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, pentyl or octyl, or a cycloalkyl group with three to about eight ring carbon atoms. C1-C20 straight
25 chained and branched alkyl groups and C3-C8 cycloalkyl groups are also referred to herein as "lower alkyl groups".

Aromatic groups include carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl, and heteroaryl groups such as imidazolyl, thienyl, furanyl, pyridyl, pyrimidyl, pyranyl, pyrrolyl, pyrazolyl, pyrazinyl, thiazole, oxazolyl and
30 tetrazole.

Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. Examples include benzothienyl, benzofuranyl, indolyl, quinolinyl, benzothiazole, benzooxazole, benzimidazole, quinolinyl, isoquinolinyl, isoindolyl,
 5 3-isoindolyl.

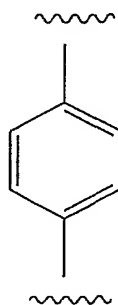
Non-aromatic heterocyclic rings are non-aromatic carbocyclic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered. Examples include tetrahydrofuranyl, tetrahyrothiophenyl, morpholino, thiomorpholino, pyrrolidinyl, piperazinyl,
 10 piperidinyl, and thiazolidinyl.

Suitable substituents on a aliphatic, aromatic non-aromatic heterocyclic or benzyl group are those which do not substantially interfere with the reactions described herein. "Interfering with a reaction" refers to substantially decreasing the yield (e.g., a decrease of greater than 50%) or causing a substantial amount of by-product formation (e.g., where by-products represent at least 50% of the theoretical yield). Interfering substituents can be used, provided that they are first converted to a protected form. Suitable protecting groups are known in the art and are disclosed, for example, in Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (1991). Suitable substituents on an aliphatic group, non-aromatic
 20 heterocyclic group, benzylic or aryl group (carbocyclic and heteroaryl) include, for example, -OH, halogen (-Br, -Cl, -I and -F), -OR^a, -O-COR^a, -COR^a, -CN, -NO₂, -COOH, -SO₃H, -NH₂, -NHR^a, -N(R^aR^b), -COOR^a, -CHO, -CONH₂, -CONHR^a, -CON(R^aR^b), -NHCOR^a, -NRCOR^a, -NHCONH₂, -NHCONR^aH, -NHCON(R^aR^b), -NR^cCONH₂, -NR^cCONR^aH, -NR^cCON(R^aR^b), -C(=NH)-NH₂, -C(=NH)-NHR^a,
 25 -C(=NH)-N(R^aR^b), -C(=NR^c)-NH₂, -C(=NR^c)-NHR^a, -C(=NR^c)-N(R^aR^b), -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR^a, -NH-C(=NH)-N(R^aR^b), -NH-C(=NR^c)-NH₂, -NH-C(=NR^c)-NHR^a, -NH-C(=NR^c)-N(R^aR^b), -NR^dH-C(=NH)-NH₂, -NR^d-C(=NH)-NHR^a, -NR^d-C(=NH)-N(R^aR^b), -NR^d-C(=NR^c)-NH₂, -NR^d-C(=NR^c)-NHR^a, -NR^d-C(=NR^c)-N(R^aR^b), -NHNH₂,
 30 -SO₂NH₂, -SO₂NHR^a, -SO₂NR^aR^b, -CH=CHR^a, -CH=CR^aR^b, -CR^c=CR^aR^b, -CR^c=CHR^a, -CR^c=CR^aR^b, -CCR^a, -SH, -SO_kR^a (k is 0, 1 or 2) and

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-NH-C(=NH)-NH₂. R^a-R^d each are independently an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group, preferably an alkyl, benzylic or aryl group. In addition, -NR^aR^d, taken together, can also form a substituted or unsubstituted non-aromatic heterocyclic group. A benzylic group, non-
5 aromatic heterocyclic group or aryl group can also have an aliphatic or substituted aliphatic group as a substituent. A substituted alkyl or aliphatic group can also have a non-aromatic heterocyclic ring, a substituted a non-aromatic heterocyclic ring, benzyl, substituted benzyl, aryl or substituted aryl group as a substituent. A
substituted aliphatic, non-aromatic heterocyclic group, substituted aryl, or
10 substituted benzyl group can have more than one substituent.

The term "arylene" refers to an aryl group which is connected to the remainder of the molecule by two other bonds. By way of example, the structure of a 1,4-phenylene group is shown below:



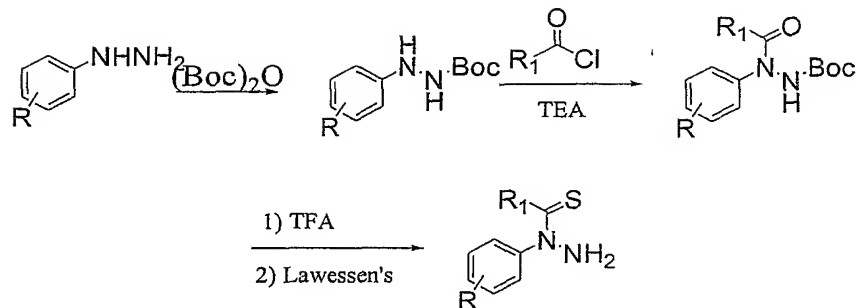
15 Substituents for an arylene group are as described below for an aryl group.

The present invention is illustrated by the following examples, which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1

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Preparation of Thiocyclohexanoic acid N-phenylhydrazide

Phenyl hydrazine (5.4g, 50 mmol) was dissolved in dry dichloromethane (50 mL) in a 250 mL round bottom flask. Di-*tert*-butyl dicarbonate (10.9 g, 50 mmol) was then added with stirring at 0 °C. The resultant solution was then stirred under reflux for 3 h. Removal of the volatile components under reduced pressure afforded a colorless solid, which was washed with hexane and dried in vacuo. 10 g (yield 96%) of the product was obtained as a colorless solid, which can be used in the next step without further purification. 2.5 g (12 mmol) of this material was dissolved in dry pyridine (5 mL). Cyclohexanecarbonyl chloride (2.0 mL, 15 mmol) was then added slowly at 0 °C. The red solution was stirred at 0 °C for half an hour and the resultant yellow suspension was stirred at room temperature for 3 h before pouring into ice-H₂O (100 mL). The precipitate product was collected by filtration and washed thoroughly with H₂O. After one recrystallization from EtOH/H₂O, 3.63 g (95%) of N-Phenyl-N-Cyclohexyl-N'-*tert*-butoxycarbonylhydrazide was obtained as a white powder; mp 141-143 °C; ¹H NMR (CDCl₃) δ 0.9-2.3 (m, 11H), 1.4 (s, 9H), 6.9 (br, 1H), 7.4 (m, 5H)ppm.

To a solution of N-Phenyl-N-Cyclohexyl-N'-*tert*-butoxycarbonylhydrazide (1.1 g, 3.46 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (6 mL) at 0 °C. The resultant solution was stirred at 0 °C for half an hour. Volatile components were then removed under reduced pressure to afford a syrup, which was turned into a solid upon standing; this material was briefly mixed with cold 2 N NaOH (5 mL) for a few minutes at 0 °C. Solid product was then collected by

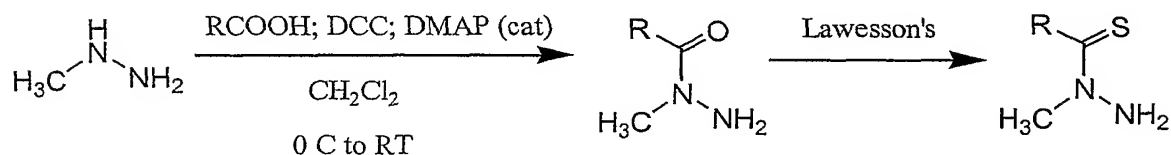
-14-

filtration and recrystallized from hexane to afford cyclohexanoic acid N-phenylhydrazide (0.6 g, 80% yield) as a white powder; ^1H NMR (DMSO-d_6) δ 0.8-3.2 (m, 1H), 5.3 (s, 2H), 7.0-7.7 (m, 5H); ESMS calcd ($\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$): 218.3; found: 241.1 ($\text{M} + \text{Na}$) $^+$.

- 5 A mixture of cyclohexanoic acid N-phenylhydrazide (0.25 g, 1.15 mmol) and Lawesson's Reagent (0.46 g, 1.15 mmol) in dry toluene (20 mL) was stirred under reflux for 1 h. After being cooled to room temperature, the mixture was filtered through a short column of silica gel (5 g) which was pre-washed with benzene. Removal of benzene afforded the crude product as a solid which was purified by
- 10 column chromatography on silica gel using hexane/EtOAc (4 : 1 v/v) as eluant. 0.15g (60%) of thiocyclohexanoic acid N-phenylhydrazide was obtained as an off white solid. ^1H NMR (CDCl_3) δ 0.8-2.4 (m, 11H), 5.65 (br, 1H), 7.1-7.6 (m, 5H); ESMS calcd ($\text{C}_{13}\text{H}_{18}\text{N}_2\text{S}$): 234.1; found: 235.1 ($\text{M} + \text{H}$) $^+$.

Example 2

15

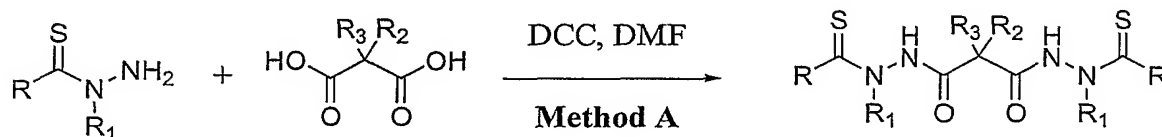


- Preparation of 2,5-Dimethoxythiobenzoic acid N-methylhydrazine: DCC (4.5g, 21.8 mmol) was added in one portion to a solution of 2,5-dimethoxybenzoic acid (3.6g, 20 mol), methylhydrazine (1.2 ml, 23 mmol) and DMAP (30 mg, cat.) in CH_2Cl_2 (60
- 20 ml) cooled in an ice bath. The reaction mixture was stirred overnight at room temperature. The slurry was cooled at -20°C for 1 h and filtered. The CH_2Cl_2 solution was evaporated and the residue was dried in vacuum. The resulting crude product was dissolved in toluene (50 ml). To this solution was added Lawesson's reagent (5.8 g, 14 mmol). The mixture was refluxed for 40 min, cooled to room
- 25 temperature, and directly subjected to silica gel column chromatography (eluent: 25 % to 35 % ethyl acetate in hexanes) to give the 2,5-dimethoxythiobenzoic acid N-

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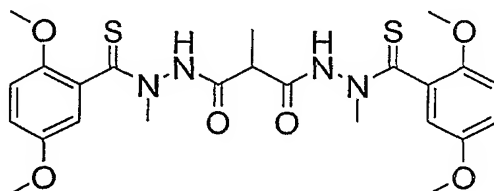
methylhydrazide (3.7 g, yield: 82%) as off-white solid. ^1H NMR (300MHz, CDCl_3): δ 6.88-6.80(m, 3H), 5.46 (s, 2H), 3.84(s, 3H), 3.82 (s, 3H), 3.28(s, 3H).

Example 3



- 5 Preparation of N-Malonyl-bis[N'-methyl-N'-(thiobenzoyl)]hydrazide: To a stirred solution of thiobenzoic acid N-methylhydrazide (0.166 g, 10 mmol), HOBT·H₂O (0.15 g, 11 mmol) and malonic acid (0.052 g, 5 mmol) in DMF (2 mL) was added DCC (0.22 g, 10.7 mmol) at 0 °C. The resultant suspension was stirred at 0 °C for 1 h and at room temperature for 3 h. Precipitated material was filtered off and washed
- 10 with EtOAc (3 x 15 mL). Combined filtrate and washings was washed successively with H₂O (2 x 20 mL), 5% citric acid (20 mL), H₂O (20 mL), Saturated NaHCO₃ (20 mL) and brine (20 mL). After being dried over Na₂SO₄, the solvent was removed under reduced pressure to afford the crude product as a yellow solid, which was washed with warm EtOAc. 0.16 g (yield 80%) of pure product was obtained as a
- 15 yellow powder. R_f 0.3 (Hexane/EtOAc 1:1 v/v); ^1H NMR (CDCl_3) δ 3.1 – 3.8 (m, 6H), 3.4 (s, 2H), 7.1 – 7.45 (m, 10 H), 9.5 – 10.5 (m, 1H) ppm; ESMS calcd ($\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$): 400.1; found: 399.1 (M-H)⁺.

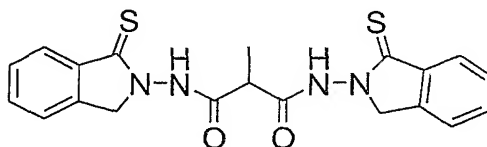
- 20 Preparation of N-(2-Methylmalonyl-bis{N'-methyl-N'-[(2,5-dimethoxy)thiobenzoyl]}hydrazide:



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DCC (4 g, 19 mmol) was added to a solution of 2,5-dimethoxythiobenzoic acid N-methylhydrazide (3.7 g, 16.4 mmol) and 2-methylmalonic acid (2 g, 17 mmol) in DMF (20 ml) with stirring at 0° C. The reaction mixture was stirred for 1 h at room temperature. The slurry was cooled at -20° C for 1 h and filtered. The filtrate was diluted with EtOAc (300 ml), washed with water (50 ml x 3), dried with Na₂SO₄. The EtOAc solution was concentrated to minimum volume, and subjected to silica gel column chromatography (eluent: 1:4 to 2:1, ethyl acetate: hexanes) to give the title compound (3.5 g, 80 %) as yellow powder. ¹H NMR (CDCl₃) δ 10.12-9.14 (2H), 7.12-6.81 (m, 6H), 4.01-3.78(m, 6H), 3.75-3.22(m, 6H), 2.82-2.62(m, 1H), 1.12-0.11(m,3H); ESMS calcd (C₂₄H₃₀N₄O₆S₂):534.16; found: 535.1 (M+H).

Preparation of 2-Methylmalonyl-bis(2-Amino-2,3-dihydro-isoindole-1-thione)

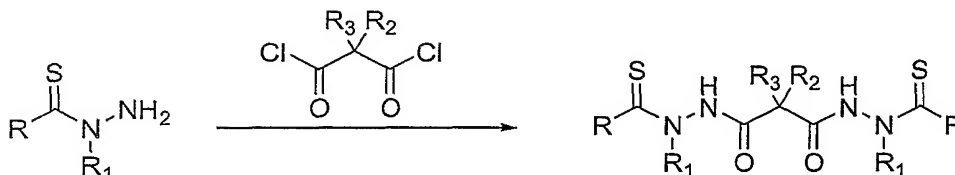


2-carboxybenzaldehyde (150 mg, 1mmol) and carbazic acid (132 mg, 1 mmol) in 40 ml methanol was stirred at room temperature for 4 h. To this solution was added Pd/C (60 mg, containing 50 % H₂O), the reaction was under H₂ atmosphere for 3 h. The reaction mixture was filtered, and the solvent was evaporated. The resulting residue was subjected to silica gel column chromatography (eluent: 20% to 50 %, EtOAc in hexanes) to yield 50 mg of product. ¹H NMR (300MHz, CDCl₃): 8.71-7.45 (m, 4H), 4.78 (s, 2H), 1.61(s, 9H). The resulting product was dissolved in CF₃COOH (5ml), stirred for 30 min. The CF₃COOH was evaporated, and the residue was subjected to silica gel column chromatography (eluent: 50% to 0%, hexanes in EtOAc) to give 2-amino-2,3-dihydro-isoindol-1-one (26mg) as a white solid. ¹H NMR (300MHz, CDCl₃): 7.85-7.39 (m, 4H), 4.54 (s, 2H). MS: 149 (M+H). Subsequent Lawesson's thiolation and DCC coupling with 2-methylmalonic acid under conditions described above afforded 2-methylmalonyl-bis(2-amino-2,3-dihydro-isoindole-1-thione) as a yellow powder. ¹H NMR (CDCl₃) δ 10.35 (s,

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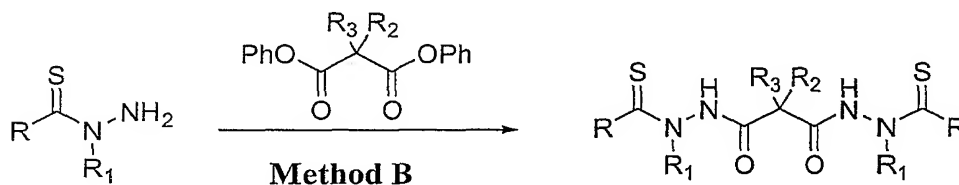
2H), 8.21-7.51(m, 8H), 5.15(s, 4H), 1.62 (s, 3H); ESMS calcd ($C_{20}H_{18}N_4O_2S_2$): 410.09; found: 411.1 (M+H).

Example 4



- 5 Preparation of N-Malonyl-bis[N¹-methyl-N¹-(thiobenzoyl)hydrazide]: To a solution of thiobenzoic acid N-methylhydrazine (10 g) stirred at 0 C were added subsequently triethylamine (8.5 mL) and malonyl dichloride (3.05 mL). The reaction mixture was stirred for 10 min, washed with water (3x50 mL), dried over sodium sulfate and concentrated. Purification by recrystallization from methylene dichloride (35 mL) gave
- 10 the product as light yellow crystals (9.0 g, 75%).

Example 5



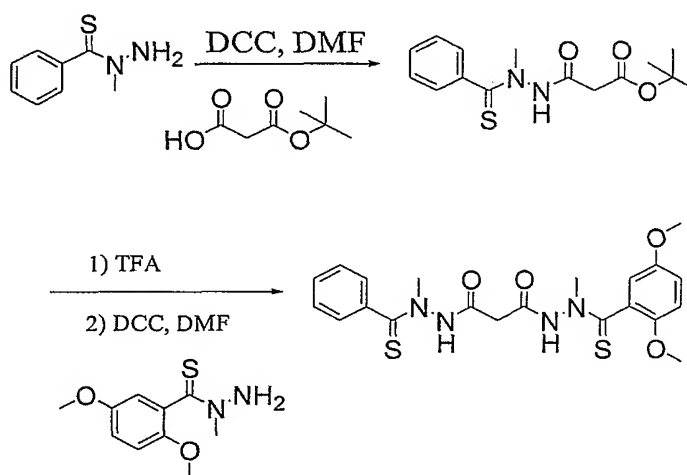
- Preparation of N-Malonyl-bis[N¹-methyl-N¹-(thiobenzoyl)hydrazide]: A stirred solution of thiobenzoic acid N-methylhydrazide (1.66 g, 10 mmol) and diphenyl malonate (1.30 g,
- 15 5.08 mmol) in dry THF (100 mL) was heated to reflux for 72 h. Volatile components were then removed under reduced pressure. The crude product was purified by column

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chromatography on silica gel using a mixture of hexane and EtOAc as eluant (gradient from 4:1 v/v to 1: 1 v/v). 1.07 g (51% yield) of pure product N-malonyl-bis[N'-methyl-N'-(thiobenzoyl)hydrazide] was obtained as a yellow powder. The physical properties of this compound was identical to the same product by obtained by the synthetic route

5 described above.

Example 6



A slurry of thiobenzoic acid N-methylhydrazide (1.0 g, 6 mmol), mono-tert-butyl malonate (1.0 mL, 6 mmol), HOBT·H₂O (0.98 g, 7.2 mmol), and DCC (1.34 g, 6.5 mmol) in DMF (5 mL) was stirred at 0 °C for 3 h and then at room temperature for 3h.

10 Precipitated material was filtered off and washed with EtOAc (3 x 20 mL). Combined filtrate and washings was washed successively with H₂O (2 X 20 mL), 5% citric acid (20 mL), H₂O (20 mL), saturated NaHCO₃ (20 mL) and brine (20 mL). After being dried over Na₂SO₄, the solvent was removed under reduced pressure to afford the crude product as a

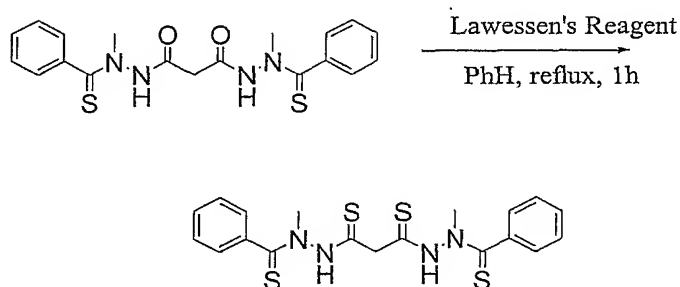
15 solid, which was washed with Et₂O. 0.94 g (yield 51%) of pure product N'-methyl-N'-(thiobenzoyl-hydrazinocarbonyl)-acetic acid *tert*-butyl ester was obtained as a yellow powder. ¹H NMR (CDCl₃) δ 1.6-1.7 (ds, 9H), 3.1-4.1 (m, 5 H), 7.3-7.7 (m, 5H), 9.7-10.3

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(ds, 1H)ppm; ESMS calcd ($C_{15}H_{20}N_2O_3S$): 308; found: 307 (M-H)⁺.

A solution of N'-Methyl-N'-thiobenzoyl-hydrazinocarbonyl)-acetic acid *tert*-butyl ester (0.19g, 0.6 mmol) and TFA (0.12 mL, 1.6 mmol) in dry DCM (10 mL) was stirred at 10 °C – 15 °C for 12 h (reaction was monitored by TLC). Volatile components were removed under reduced pressure (bath temperature below 5 °C). After being dried in vacuo, DMF (3 mL) was added followed by the addition of DCC (0.13 g, 0.6 mmol), HOBT·H₂O (93 mg, 0.7 mmol) and Thio-2,5-dimethoxybenzoic acid N-methylhydrazide (0.13 g, 0.57 mmol). The resultant solution was stirred at 0 °C for half an hour and then at room temperature for 3h. Precipitated material was filtered off and washed with EtOAc (3 x 10 mL). Combined filtrate and washings was washed successively with H₂O (2 x 10 mL), 5% citric acid (10 mL), H₂O (10 mL), Saturated NaHCO₃ (20 mL) and brine (20 mL). After being dried over Na₂SO₄, the solvent was removed under reduced pressure to afford the crude product as an oil, which was purified by SGC (4:1 hexane/EA to 2:1 EtOAc/Hexane). 0.14 g (yield 53%) of pure product was obtained as a yellow powder. ¹H NMR (CDCl₃) δ 3.1-3.9 (m, 18H), 6.7-7.4 (m, 9H)ppm; ESMS calcd ($C_{21}H_{24}N_4O_4S_2$): 460.1; found: 461.1 (M+H)⁺.

Example 7

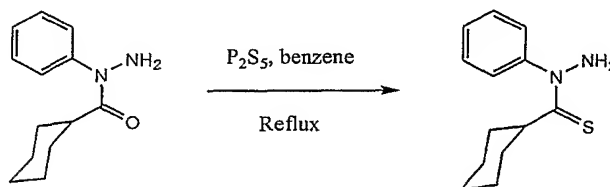


A stirred mixture of N-malonyl-bis-[N'-phenyl-N'-(thioacetyl)hydrazide] (0.1 g, 0.25 mmol) and Lawesson's reagent (0.15 g, 0.37 mmol) in dry benzene (20 mL) was heated to reflux for 1 h. After being cooled to room temperature, the mixture was filtered

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through a layer of silica gel, washed with THF (2 x 15 mL). The filtrate and washings were combined and concentrated under reduced pressure. Flush column chromatography on silica gel (hexane to 4:1 hexane/EtOAc to 2:1 hexane/EtOAc) afforded N-bisthiomalonyl-bis[N'-phenyl-N'-thioacetyl]hydrazide as a clear syrup (16 mg, 15%). ¹H NMR (CDCl₃) δ 3.80-3.95 (m, 8H), 7.02-7.30 (m, 10 H). ESMS calcd (C₁₉H₂₀N₄S₄): 432.06; found: 433.0 (M+H)⁺.

Example 8

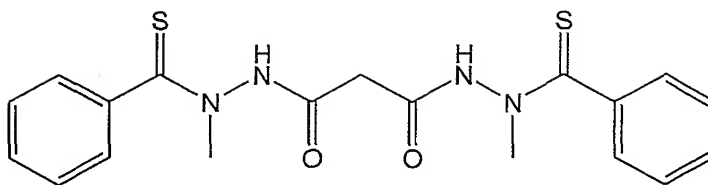


To a stirred solution of Cyclohexanoic acid N-phenylhydrazide (0.1 g, 0.45 mmol) in dry benzene (5 mL) was added P₂S₅ (0.2 g, 0.45 mol). The resultant suspension was heated to reflux for 3 h. After being cooled to room temperature, the mixture was diluted with benzene (5 mL) and was filtered through a short column of silica gel (2 g), washed with benzene and 2:1 hexane/EtOAc (15 mL each). The filtrate and washings were combined and concentrated to afford a solid. Crystallized from hexane to provide the intermediate thiocyclohexanoic acid N-phenylhydrazide as an off white solid; ¹H NMR (CDCl₃) δ 0.8-2.4 (m, 11H), 5.65 (br, 1H), 7.1-7.6 (m, 5H); ESMS calcd (C₁₃H₁₈N₂S): 234.1; found: 235.1 (M+H)⁺.

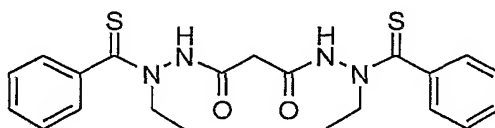
Example 9

The compounds shown below were prepared by the procedures described above. Analytical data is provided for these compounds.

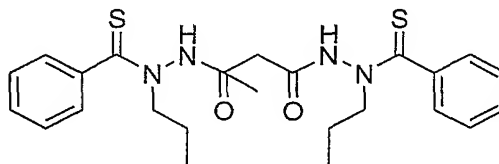
-21-



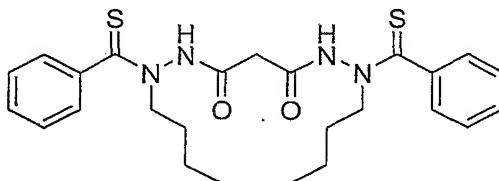
^1H NMR (CDCl_3) δ 3.1 – 3.8 (m, 6H), 3.4 (s, 2H), 7.1 – 7.45 (m, 10 H), 9.5 – 10.5 (m, 1H) ppm; ESMS calcd ($\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$): 400.1; found: 399.1 (M-H) $^+$.



- 5 ^1H NMR (CDCl_3) δ 1.0-1.35 (m, 6H), 3.0-4.3 (m, 6H), 7.05-7.40 (m, 10H), 9.1-10.1 (m, 2H); ESMS calcd ($\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2\text{S}_2$): 428.8; found: 427 (M-H) $^+$. Anal Calc For $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2\text{S}_2$ (428.13) C, 58.85; H, 5.64; N, 13.07; S, 14.96. Found: C, 58.73; H, 5.62; N, 12.97; S, 14.96.

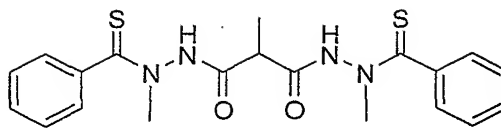


- 10 ^1H NMR (CDCl_3) δ 0.7-1.0 (m, 6H), 1.4-1.9 (m, 4H), 3.1-4.2 (m, 6H), 7.1-7.4 (m, 10H), 8.9-10.2 (m, 2H) ppm; ESMS ($\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$): 456.1; found: 455.1 (M-H) $^+$.



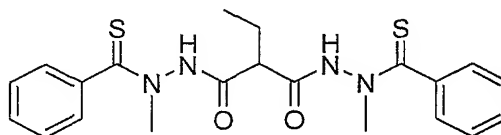
- mp 141 – 143 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 0.6-1.05 (m, 6H), 1.1-1.9 (m, 8H), 3.0-4.2 (m, 6H), 7.0-7.35 (m, 10H), 8.9-11 (ms, 2H). ESMS ($\text{C}_{25}\text{H}_{32}\text{N}_4\text{O}_2\text{S}_2$): 484.2; found: 483.1 (M-H) $^+$.
 15 Anal Calc For $\text{C}_{25}\text{H}_{32}\text{N}_4\text{O}_2\text{S}_2$ (484.2) C, 61.95; H, 6.65; N, 11.56; S, 13.23. Found: C, 61.98; H, 6.52; N, 11.26; S, 13.16.

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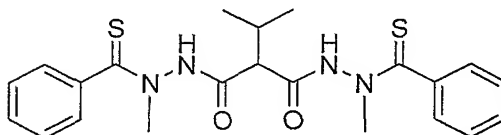


^1H NMR (DMSO- d_6) δ 0.4-0.9 (dd, 3H, $J = 7$), 2.7 (q, 1H), 3.1 – 3.6 (m, 6H), 7.1 – 7.5 (m, 10H), 10.9 (br, 2H)ppm; ESMS ($\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2\text{S}_2$): 414; found: 413 (M-H) $^+$.

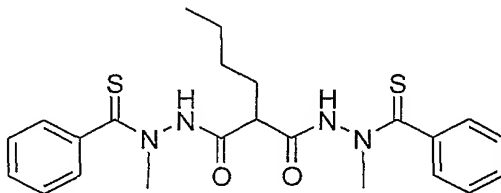
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^1H NMR (CDCl_3) δ 0.5 (t, 3H, $J = 7$), 1.1-1.6 (m, 2H), 2.7 (t, 1H, $J = 7$), 3.1 – 3.3 (m, 6H), 7.0-7.3 (m, 10H), 10.25 (s, 2H) ppm; MS ($\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2\text{S}_2$): 428.1; found: 427.1 (M-H) $^+$.

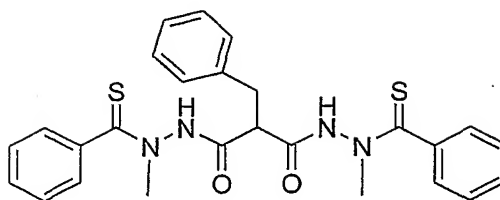


10 ^1H NMR (CDCl_3) δ 0.5 (d, 6H, $J = 7$), 0.9-1.2 (m, 1H), 3.0-4.1 (m, 7H), 7.1-7.4 (m, 10H), 10.3 (s, 2H)ppm; ESMS ($\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$): 442.1; found: 441.1 (M-H) $^+$.

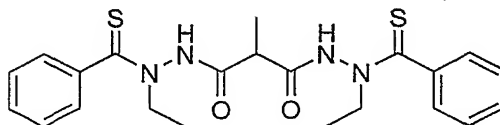


15 ^1H NMR (CDCl_3) δ 0.4-1.3 (m, 5H), 1.5-1.8 (m, 2H), 3.0-3.7 (m, 6H), 7.1-7.5 (m, 10H), 11 (s, 2H)ppm; MS ($\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$): 456.1; found: 455.1 (M-H) $^+$.

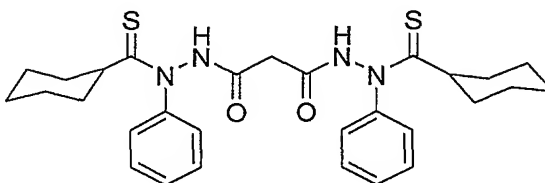
-23-



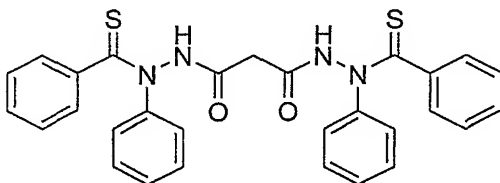
^1H NMR (CDCl_3) δ 2.1 (d, 2H, $J=7$), 2.9 (t, 1H, $J=7$), 3.1-3.5 (m, 6H), 6.8-7.4 (m, 15H), 11 (s, 2H)ppm; MS ($\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$): 490.1; found: 489.1 (M-H) $^+$.



- 5 ^1H NMR (CDCl_3) δ 0.4 (d, 3H, $J=7$), 1.0-1.4 (m, 6H), 2.75 (q, 1H), 3.0-4.3 (m, 4H), 7.1-7.4 (m, 10H), 10.6 (s, 2H); ESMS Calc For ($\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$): 442.1; found: 441.1 (M-H) $^+$; Anal Calc For $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$ (442.15) C, 59.70; H, 5.92; N, 12.66; S, 14.49. Found: C, 59.64; H, 5.92; N, 12.59; S, 14.47.

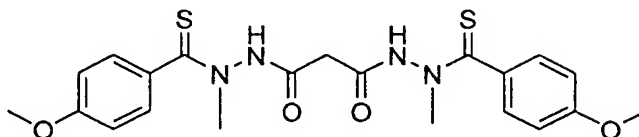


- 10 ^1H NMR (DMSO-d_6) δ 0.9-1.8m, 22H), 3.1-3.5 (m, 2H), 7.2-7.6 (m, 10H), 11.1 – 11.7 (ms, 2H) ppm; ESMS calcd ($\text{C}_{29}\text{H}_{36}\text{N}_4\text{O}_2\text{S}_2$):536.3; found: 537.3(M-H) $^+$.

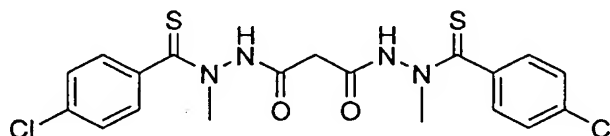


-24-

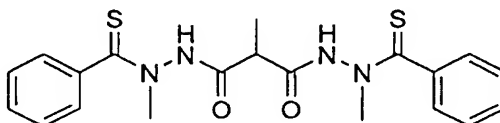
^1H NMR ($\text{DMSO}-d_6$) δ 3.20 (br, 2H), 7.1-7.6 (m, 20 H), 11.5 (s, 2H)ppm; ESMS calcd ($\text{C}_{29}\text{H}_{24}\text{N}_4\text{O}_2\text{S}_2$): 524.1; found: 523.1 ($\text{M}-\text{H}$) $^+$.



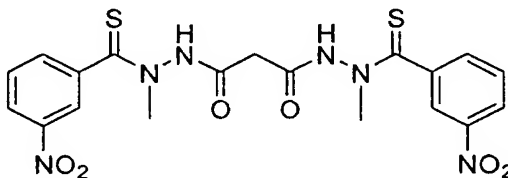
^1H NMR (CDCl_3) δ 3.0-4.3 (m, 14H), 6.6-7.5 (m, 8H), 10.4 (s, 2H) ppm; ESMS calcd
5 ($\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2\text{S}_2$): 460.2; found: 461.2 ($\text{M}+\text{H}$) $^+$.



^1H NMR (CDCl_3) δ 2.65-3.60 (m, 8H), 7.2-7.4 (m, 8H), 11.1 (br, 2H); ESMS calcd ($\text{C}_{19}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_2\text{S}_2$): 468.0; found: 467.9 ($\text{M}-\text{H}$) $^+$.



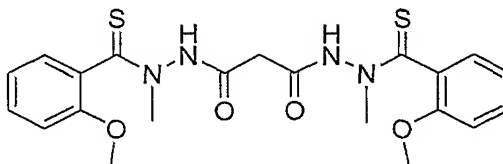
10 ^1H NMR (CDCl_3) δ 0.4 (d, 3H, $J = 7$), 2.7 (q, 1H, $J = 7$), 3.0-3.8 (m, 6H), 7.2-8.2 (m, 8H), 10.5-10.7 (ms, 2H) ppm; ESMS calcd ($\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_2\text{S}_2$): 482.0; found: 481.0 ($\text{M}-\text{H}$) $^+$.



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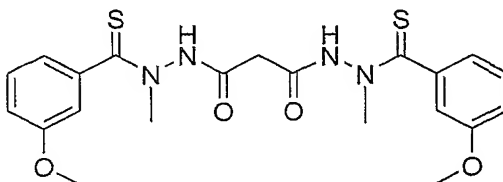
^1H NMR (CDCl_3) δ 2.9-3.8 (m, 6H), 7.3-7.7 (m, 4H), 8.0-8.3 (m, 4H), 10.9 (s, 2H);

ESMS calcd ($\text{C}_{10}\text{H}_{18}\text{N}_6\text{O}_6\text{S}_2$): 490.0; found: 489.0 (M-H) $^+$.



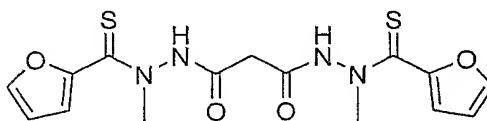
^1H NMR (CDCl_3) δ 3.1-3.9 (m, 14H), 6.7-7.8 (m, 8H), 9.0-10 (m, 2H) ppm; ESMS calcd

5 ($\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_4\text{S}_2$): 460.1; found: 459.1 (M-H) $^+$.



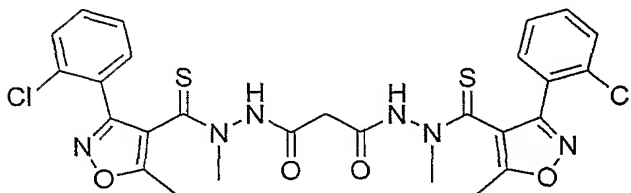
(SBR-11-5032): ^1H NMR (CDCl_3) δ 3.0-3.9 (m, 14H), 6.7-7.3 (m, 8H), 9.0-10 (m, 2H)

ppm; ESMS calcd ($\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_4\text{S}_2$): 460.1; found: 459.1 (M-H) $^+$.



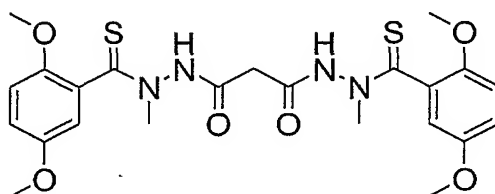
10 ^1H NMR (acetone- d_6) δ 3.5 (s, 2H), 6.45 (d, 2H, $J = 5$), 6.9 (d, 2H, $J = 5$), 7.2-7.6 (m,

12H), 10.6 (s, 2H) ppm; ESMS calcd ($\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_4\text{S}_2$): 504.1; found: 503.1 (M-H) $^+$.

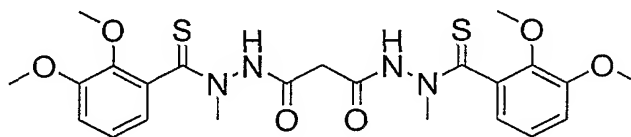


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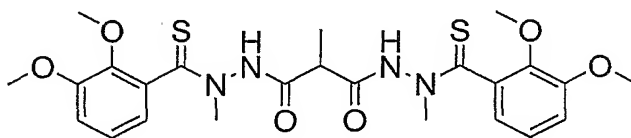
^1H NMR (DMSO- d_6) δ 2.60 (s, 6H), 3.05 (s, 6H), 3.40 (s, 2H), 7.15-7.50 (m, 8H)ppm;
 ESMS calcd ($\text{C}_{27}\text{H}_{24}\text{Cl}_2\text{N}_6\text{O}_4\text{S}_2$): 630.1; found: 629.1 (M-H) $^+$.



^1H NMR (CDCl_3) δ 10.06-8.82 (2H), 7.16-6.81(m,6H), 4.01-3.81(m, 6H), 3.78-
 5 3.11(m,6H), 2.81-2.58(m,2H): ESMS calcd ($\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_6\text{S}_2$): 520.15; found: 521 (M+H).



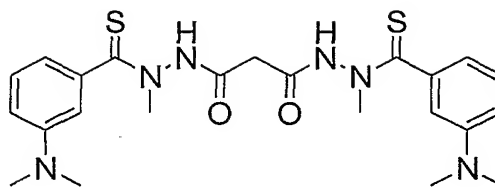
^1H NMR (CDCl_3) δ 10.38-9.01 (2H), 7.12-6.82 (m, 6H), 3.92-3.78(m, 12H), 3.75-
 3.06(m, 6H), 2.61-2.51 (m, 2H); ESMS calcd ($\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_6\text{S}_2$): 520.15; found: 521
 (M+H).



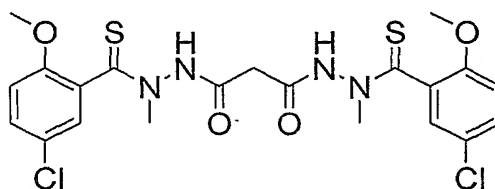
10

^1H NMR (CDCl_3) δ 9.45-8.63 (2H), 7.18-6.81 (m, 6H), 4.01-3.80(m, 6H), 3.78-3.24(m,
 6H), 2.62-2.50(m, 1H), 1.74-0.11 (m, 3H); ESMS calcd ($\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_6\text{S}_2$):534.16; found:
 535 (M+H).

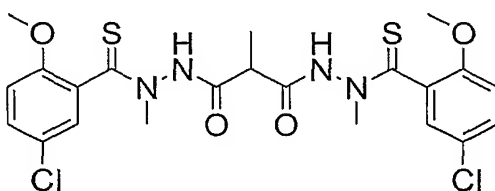
-27-



^1H NMR (CDCl_3) δ 10.19-8.61 (2H), 7.26-6.52(m, 6H), 3.81-3.08(m, 8H), 3.01-2.88(m, 12H). ESMS calcd ($\text{C}_{23}\text{H}_{30}\text{N}_6\text{O}_2\text{S}_2$): 486.19; found: 487 (M+H).

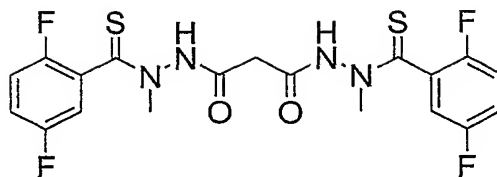


- 5 ^1H NMR (CDCl_3) δ 9.92-8.80 (2H), 7.41-6.72 (m, 6H), 4.01-3.81(m,6H), 3.80-3.15 (m,6H), 2.76-2.42(m, 2H); ESMS calcd ($\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{N}_4\text{O}_4\text{S}_2$):528.05; found: 529(M+H).

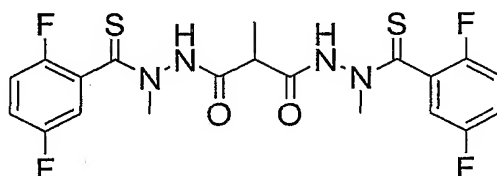


- 10 ^1H NMR (CDCl_3) δ 10.21-9.02(2H), 7.60-6.81 (m, 6H), 4.14-3.88(m, 6H), 3.87-3.18 (m,6H), 2.84-2.65(m, 1H),1.10-0.16 (m, 3H); ESMS calcd ($\text{C}_{22}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_4\text{S}_2$): 542.06; found: 543(M+H).

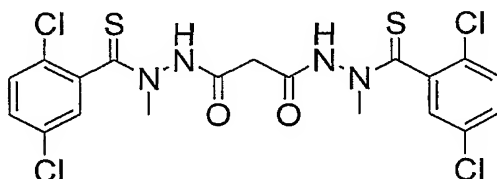
-28-



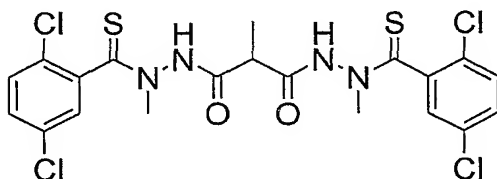
^1H NMR (CDCl_3) δ 10.02-9.20 (2H), 7.63-7.01 (m, 6H), 4.21-3.22 (m, 6H), 1.88-1.36 (m, 2H); ESMS calcd ($\text{C}_{19}\text{H}_{16}\text{F}_4\text{N}_4\text{O}_2\text{S}_2$): 472.07; found: 473 (M+H).



5 ^1H NMR (CDCl_3) δ 7.93-7.61 (2H), 7.40-6.92 (m, 6H), 3.98-3.41 (m, 6H), 2.19-0.93 (m, 4H); ESMS calcd ($\text{C}_{20}\text{H}_{18}\text{F}_4\text{N}_4\text{O}_2\text{S}_2$): 486.08; found: 487 (M+H).

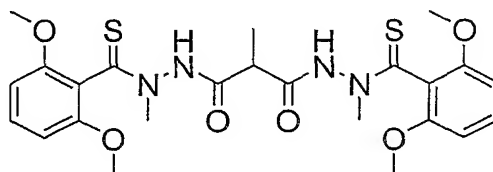


^1H NMR (CDCl_3) δ 10.12-9.21 (2H), 7.67-7.23 (m, 6H), 3.94-3.22 (m, 6H), 2.01-1.21 (m, 2H); ESMS calcd ($\text{C}_{19}\text{H}_{16}\text{Cl}_4\text{N}_4\text{O}_2\text{S}_2$): 535.95; found: 537 (M+H).

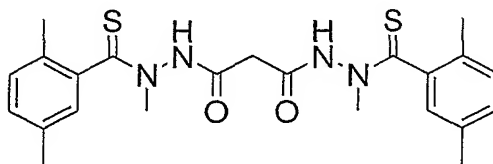


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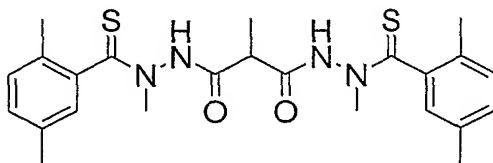
^1H NMR (CDCl_3) δ 7.78-7.23 (2H), 4.56-3.10 (m, 6H), 2.34-1.12 (m, 4H); ESMS calcd ($\text{C}_{20}\text{H}_{18}\text{Cl}_4\text{N}_4\text{O}_2\text{S}_2$): 549.96; found: 551 (M+H).



^1H NMR (CDCl_3) δ 9.92-9.01 (2H), 7.38-7.15 (m, 3H), 6.66-6.51 (m, 3H), 3.98-3.75 (m, 12H), 3.72-3.21 (m, 6H), 2.01-0.42 (m, 4H); ESMS calcd ($\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_6\text{S}_2$): 534.16; found: 535 (M+H).

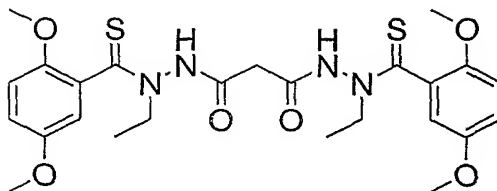


^1H NMR (CDCl_3) δ 10.51-9.82 (2H), 7.42-6.80 (m, 6H), 3.92-3.04 (m, 6H), 2.60-1.21 (m, 14H); ESMS calcd ($\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$): 456.17; found: 457 (M+H).

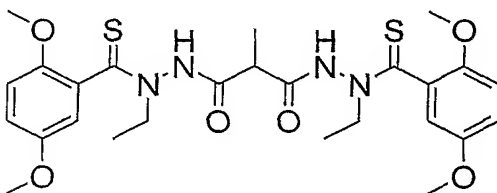


^1H NMR (CDCl_3) δ 10.51-8.82 (2H), 7.11-6.89 (m, 6H), 3.81-3.02 (m, 6H), 2.40-1.02 (m, 16H); ESMS calcd ($\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_2\text{S}_2$): 470.18; found: 471 (M+H).

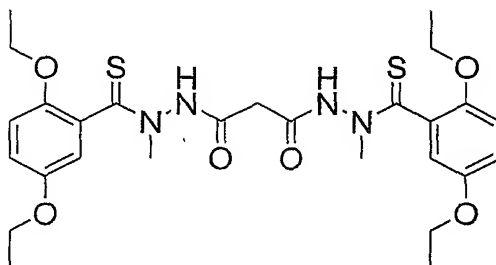
-30-



^1H NMR (CDCl_3) δ 9.86-8.42 (2H), 7.01-6.6 (m, 6H), 4.18-3.51 (m, 16H), 3.22-2.26 (2H), 1.40-1.04 (m, 6H); ESMS calcd ($\text{C}_{25}\text{H}_{32}\text{N}_4\text{O}_6\text{S}_2$):548.18; found: 547 (M-H).

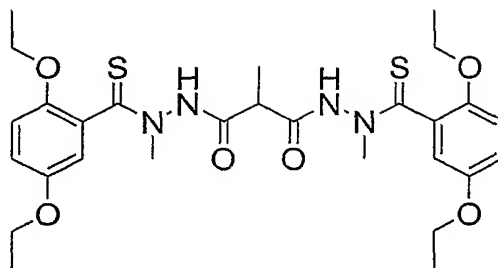


5 ^1H NMR (CDCl_3) δ 9.99-8.41 (2H), 7.01-6.68 (m, 6H), 4.18-3.56 (m, 16H), 1.40-0.02 (m, 10H); ESMS calcd ($\text{C}_{26}\text{H}_{34}\text{N}_4\text{O}_6\text{S}_2$): 562.19; found: 561(M-H).

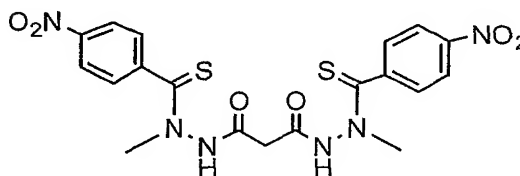


^1H NMR (CDCl_3) δ 10.12-8.82 (2H), 7.03-6.62 (m, 6H), 4.21-3.87 (m, 8H), 3.84-3.01(m, 6H), 2.71-2.42 (m, 2H), 1.56-1.21 (m, 12H); ESMS calcd ($\text{C}_{27}\text{H}_{36}\text{N}_4\text{O}_6\text{S}_2$):
 10 576.21; found: 577(M+H).

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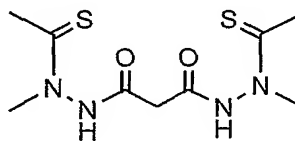


^1H NMR (CDCl_3) δ 9.81-8.79 (2H), 7.01-6.64 (m, 6H), 4.21-3.81 (m, 8H), 3.80-3.22 (m, 6H), 1.54-1.20 (m, 13H), 1.01-0.16 (m, 3H); ESMS calcd ($\text{C}_{28}\text{H}_{38}\text{N}_4\text{O}_6\text{S}_2$): 590.22; found: 591(M+H).



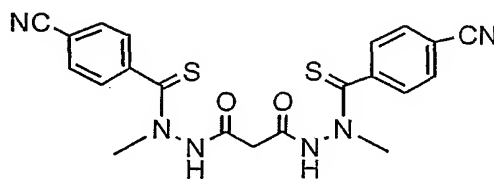
5

^1H NMR ($\text{DMSO}-d_6$): δ 8.25 (d, $J=8.1$ Hz, 4H), 7.50 (d, $J=8.1$ Hz, 4H), 3.7-3.3 (m, 8H); ESMS calcd for $\text{C}_{19}\text{H}_{18}\text{N}_6\text{O}_6\text{S}_2$: 490.1; Found: 489.0 (M-H).



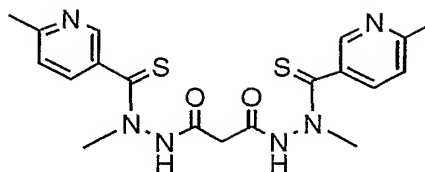
^1H NMR (CDCl_3): δ 3.6-3.4 (m, 8H), 2.7-2.5 (m, 6H); ESMS calcd for $\text{C}_9\text{H}_{16}\text{N}_4\text{O}_2\text{S}_2$: 276.1; Found: 274.9 (M-H).

10



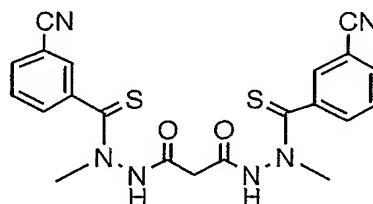
^1H NMR (CDCl_3): δ 10.25 (m, 2H), 7.7-7.4 (m, 8H), 3.7 (m, 2H), 3.35 (m, 6H); ESMS calcd for $\text{C}_{21}\text{H}_{18}\text{N}_6\text{O}_2\text{S}_2$: 450.1; Found: 449.0 (M-H).

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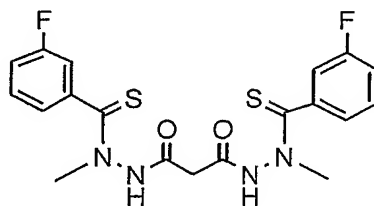


^1H NMR (CDCl_3): δ 8.2 (s, 2H), 7.7-7.5 (m, 4H), 3.7-3.4 (m, 8H), 2.9-2.8 (m, 6H);

ESMS calcd for $\text{C}_{19}\text{H}_{22}\text{N}_6\text{O}_2\text{S}_2$: 430.1; Found: 431.1 (M+H).

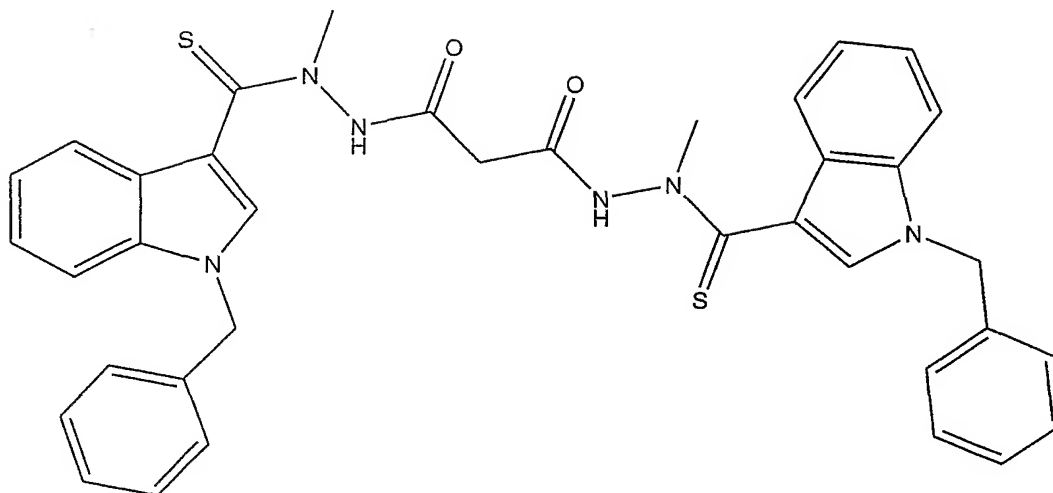


- 5 ^1H NMR (CDCl_3): δ 10.0-9.2 (m, 2H), 7.9-7.45 (m, 8H), 4.0-3.4 (m, 8H); ESMS calcd for $\text{C}_{21}\text{H}_{18}\text{N}_6\text{O}_2\text{S}_2$: 450.1; Found: 451.0 (M+H).

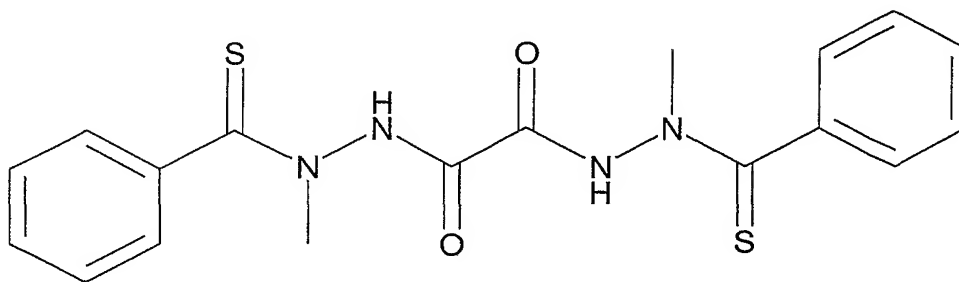


^1H NMR (CDCl_3): δ 10.1-9.4 (2H), 7.5-7.2 (m, 8H), 3.9-3.3 (m, 8H); ESMS calcd for $\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_4\text{O}_2\text{S}_2$: 436.1; Found: 437.1 (M+H).

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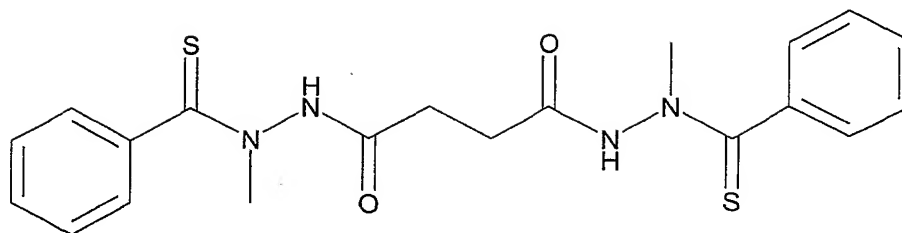
^1H NMR (CDCl_3): δ 3.3 (s, 2H), 3.6 (s, 6H), 5.25 (s, 4H), 7.05-7.3 (m, 16H), 7.6 (s, 2H), 7.9 (d, 2H, $J = 6$), 10.56 (s, 2H)ppm; ESMS calcd ($\text{C}_{37}\text{H}_{34}\text{N}_6\text{O}_2\text{S}_2$): 658.2; found: 659.2 ($\text{M}+\text{H}$) $^+$.



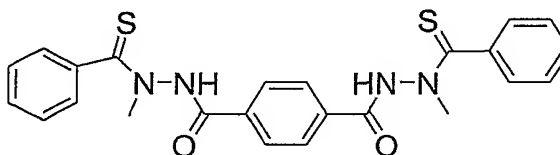
5

^1H NMR (DMSO) δ 11.98 (2H), 7.44-7.12 (m, 10H), 3.69-3.14 (s, 6H). ESMS calcd ($\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_2\text{S}_2$): 386.09; found: 387.1 ($\text{M}+\text{H}$) $^+$.

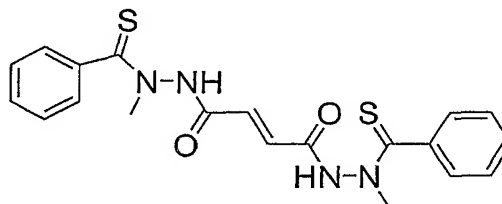
-34-



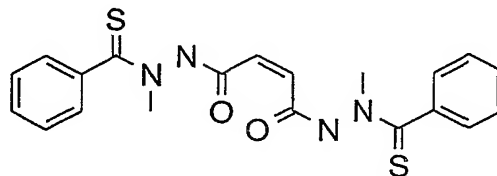
^1H NMR (CHCl_3) δ 9.48-8.55 (2H), 7.56-7.20(m, 10H), 3.80-3.31(m, 6H), 2.88-2.22(m, 4H). ESMS calcd ($\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2\text{S}_2$): 414.12; found: 415.1 (M+H).



5 ^1H NMR (300 MHz, CDCl_3) δ 10.21-9.91 (m, 2H), 8.06-7.32 (m, 14H), 3.91-3.56 (m, 6H). ESMS calcd ($\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_2\text{S}_2$): 462.12; found: 463 (M+H).

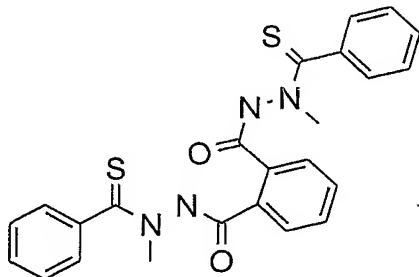


^1H NMR (300 MHz, DMSO-d_6) δ 11.60-11.40 (m, 2H), 7.48-6.46(m, 12H), 3.64-3.3.30(m, 6H). ESMS calcd ($\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$): 412.10; found: 413 (M+H).



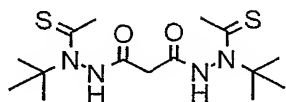
-35-

^1H NMR (300 MHz, CDCl_3) δ 7.58-7.20(m, 12H), 3.68-3.20(m, 6H). ESMS calcd ($\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$): 412.10; found: 413 (M+H).

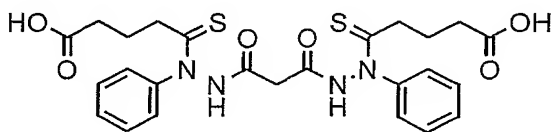


^1H NMR (300 MHz, CDCl_3) δ 9.65-8.70 (2H), 8.01-7.21(m, 14H), 3.84-3.40(m, 6H).

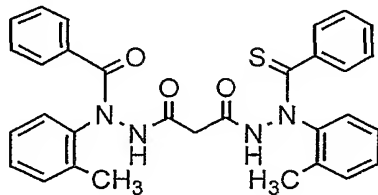
5 ESMS calcd ($\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_2\text{S}_2$): 462.12; found: 463 (M+H).



^1H NMR (CDCl_3): δ 2.63 (s, 2H); 2.18 (s, 6H); 1.25 (s, 18H). MS calcd for $\text{C}_{15}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$: 360.2; Found: 383.1 (M+Na).

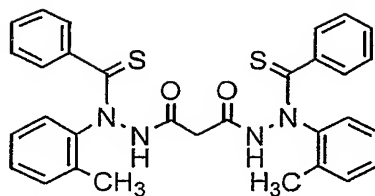


10 ^1H NMR (CDCl_3): δ 7.3 (m, 10H); 3.2 (m, 2H); 2.45 (t, J=7.4 Hz, 4H); 2.21 (t, J=7.4 Hz, 4H); 1.90 (m, 8H). MS calcd for $\text{C}_{25}\text{H}_{28}\text{N}_4\text{O}_6\text{S}_2$: 544.15; Found: 567.2 (M+Na).

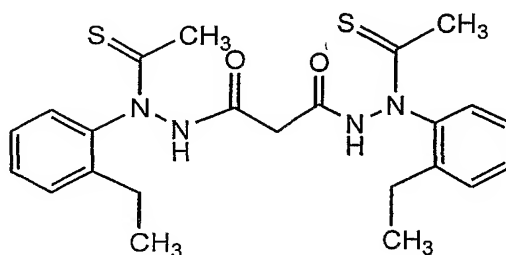


^1H NMR (CDCl_3): δ 7.4-1 (m, 18H); 3.3 (br s, 2H); 2.5 (br s, 6H). MS calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_3\text{S}$: 536.2; Found: 537.2 (M+H).

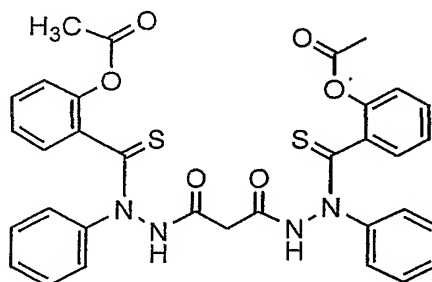
-36-



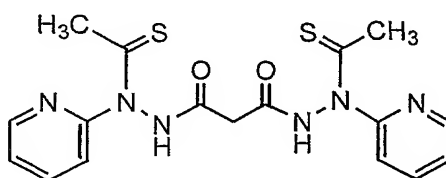
^1H NMR (CDCl_3): δ 7.2 (m, 18H); 3.5 (br s, 2H); 2.4 (br s, 6H). MS calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$: 552.2; Found: 553.2 (M+H).



5 ^1H NMR (CDCl_3): δ 7.8-7.4 (br s, 8H), 3.75-3.5 (m, 2H), 3.95-3.8 (m, 4H), 2.58 (s, 6H), 1.4 (m, 6H). ESMS calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$: 456.2; Found: 479.2 (M+Na).

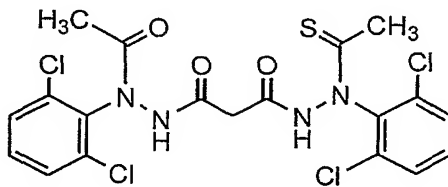


^1H NMR (CDCl_3): δ 7.5 (br s, 18H), 3.4 (br s, 2H), 2.45 (s, 6H). ESMS calcd for $\text{C}_{33}\text{H}_{28}\text{N}_4\text{O}_6\text{S}_2$: 640.1; Found 641.1 (M+H).

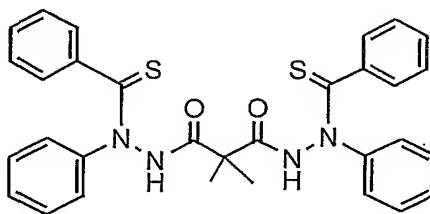


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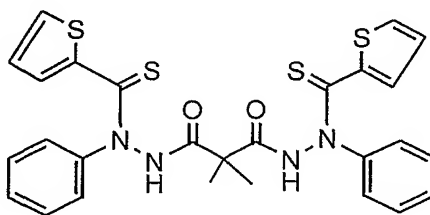
^1H NMR (CDCl_3): δ 8.3-8.05 (m, 4H), 7.75 (t, $J=8.0$ Hz, 2H), 7.1 (br s, 2H), 3.74 (s, 2H), 2.38 (s, 6H). ESMS calcd for $\text{C}_{17}\text{H}_{18}\text{N}_6\text{O}_2\text{S}_2$: 402.1. Found: 403.1 (M+H).



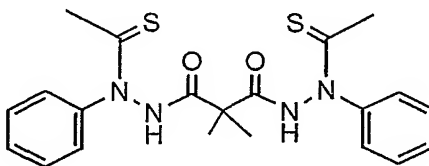
^1H NMR (CDCl_3): δ 7.7-7.2 (m, 6H), 3.2 (s, 2H), 2.58 (s, 3H), 2.15 (s, 3H). ESMS calcd for $\text{C}_{19}\text{H}_{16}\text{Cl}_4\text{N}_4\text{O}_3\text{S}$: 519.9; Found: 520.9 (M+H).



^1H NMR ($\text{CDCl}_3\text{-D}_2\text{O}$): δ 7.45-7.15 (m, 20 H), 1.6 (br s, 6H). ESMS calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$: 552.2; Found: 553.2 (M+H).

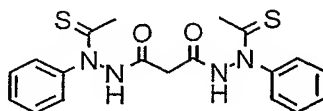


10 ^1H NMR (DMSO-d_6): δ 11.3 (s, 2H), 7.75 (d, $J=6.0$ Hz, 2H), 7.5-7.4 (m, 12 H); 6.9 (m, 2H); ESMS calcd for $\text{C}_{27}\text{H}_{24}\text{N}_4\text{O}_2\text{S}_4$: 564.1; Found: 565.2 (M+H).

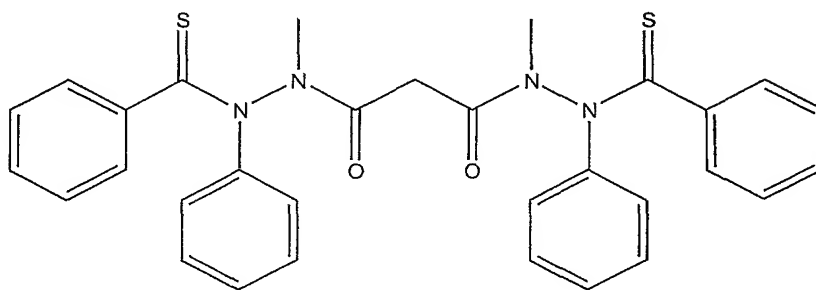


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^1H NMR (CDCl_3): δ 7.38 (m, 10 H), 2.40 (s, 6H), 1.5-1.6 (6H); ESMS calcd for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2\text{S}_2$: 564.1; Found: 565.2 ($\text{M}+\text{H}$).



^1H NMR ($\text{DMSO}-d_6$): δ 11.5 (m, 2H); 7.5 (m, 10 H); 3.2 (m, 2H); 2.6 (s, 3H); 2.5 (s, 3H). MS calcd (400.1); Found: 423.1 ($\text{M}+\text{Na}$).



^1H NMR (CDCl_3) δ 3.3-4.5 (m, 8H), 7.1-7.8 (m, 20 H)ppm; ESMS calcd ($\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}_2$): 552; found: 551 ($\text{M}-\text{H}$) $^+$.

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While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

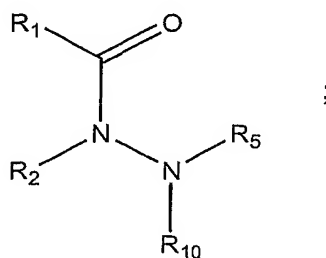
-40-

CLAIMS

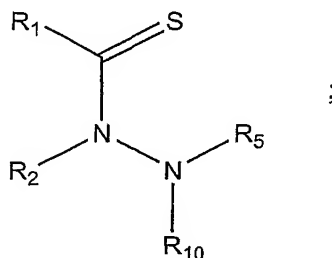
What is claimed is:

1. A method of preparing a product compound from a starting compound, wherein the starting compound is represented by the following structural formula:

5



and the product compound is represented by the following structural formula:



wherein:

10 R_1 and R_2 are independently an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group, or R_1 and R_2 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

15 R_5 is a hydrazine protecting group when R_2 is an aryl group or a substituted aryl group and R_5 is -H or a hydrazine protecting group when R_2 is an aliphatic or substituted aliphatic group;

R_{10} is -H or a substituted or unsubstituted alkyl group,

the method comprising the step of reacting the starting compound with a thionylating reagent.

2. The method of Claim 1 wherein the thionylating reagent is Lawesson's Reagent, phosphorus pentasulfide, Scheeren's Reagent ($P_4S_{10}-Na_2S$), $P_4S_{10}-N(ethyl)_3$,
5 Davy's Reagent and Heimgarner's reagent.
3. The method of Claim 2 wherein the thionylating reagent is Lawesson's Reagent.
4. The method of Claim 1 wherein R_5 is -H when R_2 is an aliphatic or substituted aliphatic group and R_{10} is -H or an unsubstituted alkyl group.
5. The method of Claim 4 wherein R_1 is an aryl group or a substituted aryl group.
- 10 6. The method of Claim 5 wherein R_2 is an alkyl group or a substituted lower alkyl group.
7. The method of Claim 6 wherein R_2 is methyl or ethyl.
8. The method of Claim 6 wherein R_1 is phenyl or substituted phenyl.
9. The method of Claim 7 wherein R_1 is phenyl and R_2 is methyl.
- 15 10. The method of Claim 8 wherein R_1 is phenyl substituted with one or more groups selected from -OH, -Br, -Cl, -I, -F, -OR^a, -O-COR^a, -COR^a, -CN, -NO₂, -COOH, -SO₃H, -NH₂, -NHR^a, -N(R^aR^b), -COOR^a, -CHO, -CONH₂, -CONHR^a, -CON(R^aR^b), -NHCOR^a, -NRCOR^a, -NHCONH₂, -NHCONR^aH, -NHCON(R^aR^b), -NR^cCONH₂, -NR^cCONR^aH, -NR^cCON(R^aR^b), -C(=NH)-NH₂, -C(=NH)-NHR^a,
20 -C(=NH)-N(R^aR^b), -C(=NR^c)-NH₂, -C(=NR^c)-NHR^a, -C(=NR^c)-N(R^aR^b), -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR^a, -NH-C(=NH)-N(R^aR^b), -NH-C(=NR^c)-NH₂, -NH-C(=NR^c)-NHR^a, -NH-C(=NR^c)-N(R^aR^b),

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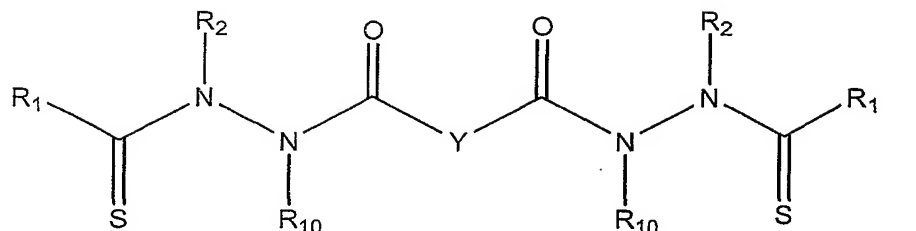
-NR^dH-C(=NH)-NH₂, -NR^d-C(=NH)-NHR^a, -NR^d-C(=NH)-N(R^aR^b),
 -NR^d-C(=NR^c)-NH₂, -NR^d-C(=NR^c)-NHR^a, -NR^d-C(=NR^c)-N(R^aR^b), -NHNH₂,
 -NHNHR^a, -NHN(R^aR^b), -SO₂NH₂, -SO₂NHR^a, -SO₂NR^aR^b, -CH=CHR^a,
 -CH=CR^aR^b, -CR^c=CR^aR^b, -CR^c=CHR^a, -CR^c=CR^aR^b, -CCR^a, -SH, -SR^a, -S(O)R^a,
 5 -S(O)₂R^a, alkyl groups, substituted alkyl group, non-aromatic heterocyclic group,
 substituted non-aromatic heterocyclic group, benzyl group, substituted benzyl
 group, aryl group or substituted aryl group wherein R^a-R^d each are independently
 an alkyl group, substituted alkyl group, benzyl, substituted benzyl, aromatic or
 substituted aromatic group, or, -NR^aR^d, taken together, can also form a substituted
 10 or unsubstituted non-aromatic heterocyclic group.

11. The method of Claim 5 wherein R₂ is a phenyl group or a substituted phenyl group.
12. The method of Claim 4 wherein R₁ is an aliphatic group or a substituted aliphatic group.
- 15 13. The method of Claim 12 wherein R₂ is a phenyl group or a substituted phenyl group.
14. The method of Claim 13 wherein R₁ is a lower alkyl group and R₂ is a phenyl group substituted with one or more groups selected from -OH, -Br, -Cl, -I, -F, -OR^a, -O-COR^a, -COR^a, -CN, -NO₂, -COOH, -SO₃H, -NH₂, -NHR^a, -N(R^aR^b),
 20 -COOR^a, -CHO, -CONH₂, -CONHR^a, -CON(R^aR^b), -NHCOR^a, -NRCOR^a,
 -NHCONH₂, -NHCONR^aH, -NHCON(R^aR^b), -NR^cCONH₂, -NR^cCONR^aH,
 -NR^cCON(R^aR^b), -C(=NH)-NH₂, -C(=NH)-NHR^a, -C(=NH)-N(R^aR^b),
 -C(=NR^c)-NH₂, -C(=NR^c)-NHR^a, -C(=NR^c)-N(R^aR^b), -NH-C(=NH)-NH₂,
 -NH-C(=NH)-NHR^a, -NH-C(=NH)-N(R^aR^b), -NH-C(=NR^c)-NH₂,
 25 -NH-C(=NR^c)-NHR^a, -NH-C(=NR^c)-N(R^aR^b), -NR^dH-C(=NH)-NH₂,
 -NR^d-C(=NH)-NHR^a, -NR^d-C(=NH)-N(R^aR^b), -NR^d-C(=NR^c)-NH₂,
 -NR^d-C(=NR^c)-NHR^a, -NR^d-C(=NR^c)-N(R^aR^b), -NHNH₂, -NHNHR^a,

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- $-\text{NHN}(\text{R}^{\text{a}}\text{R}^{\text{b}})$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHR}^{\text{a}}$, $-\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{CH}=\text{CHR}^{\text{a}}$, $-\text{CH}=\text{CR}^{\text{a}}\text{R}^{\text{b}}$,
 $-\text{CR}^{\text{c}}=\text{CR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{CR}^{\text{c}}=\text{CHR}^{\text{a}}$, $-\text{CR}^{\text{c}}=\text{CR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{CCR}^{\text{a}}$, $-\text{SH}$, $-\text{SR}^{\text{a}}$, $-\text{S}(\text{O})\text{R}^{\text{a}}$, $-\text{S}(\text{O})_2\text{R}^{\text{a}}$,
 alkyl groups, substituted alkyl group, non-aromatic heterocyclic group,
 substituted non-aromatic heterocyclic group, benzyl group, substituted benzyl
 5 group, aryl group or substituted aryl group wherein $\text{R}^{\text{a}}-\text{R}^{\text{d}}$ each are independently
 an alkyl group, substituted alkyl group, benzyl, substituted benzyl, aromatic or
 substituted aromatic group, or, $-\text{NR}^{\text{a}}\text{R}^{\text{d}}$, taken together, can also form a substituted
 or unsubstituted non-aromatic heterocyclic group.
15. The method of Claim 4 wherein R_2 is an aliphatic group or a substituted aliphatic
 10 group.
16. The method of Claim 15 wherein R_1 is a lower alkyl group or a substituted lower
 alkyl group.
17. The method of Claim 4 wherein R_2 is an aryl group or a substituted aryl group.
18. The method of Claim 17 wherein R_2 is a phenyl group or a substituted phenyl
 15 group.
19. The method of Claim 1 wherein R_5 is *tert*-butoxycarbonyl.
20. The method of Claim 4 further comprising the steps of:
 - a) deprotecting the hydrazide group of the product compound when R_5 is a
 hydrazide protecting group to form the product compound wherein R_5 is
 20 $-\text{H}$; and
 - b) reacting $\text{Z}-\text{C}(\text{O})-\text{Y}-(\text{CO})-\text{Z}$ or $\text{HO}-\text{C}(\text{O})-\text{Y}-(\text{CO})-\text{OH}$ and a carboxylic
 acid activating agent and with the product compound wherein R_5 is $-\text{H}$ to
 form a second product represented by the following structural formula:

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wherein:

Y is a covalent bond or a substituted or unsubstituted straight-chained hydrocarbyl group; and

5 each Z is a leaving group.

21. The method of Claim 20 wherein Y is a covalent bond, $-(CH_2CH_2)-$, *trans*-(CH=CH)-, *cis*-(CH=CH)-, $-(CC)-$ or a 1,4-phenylene group.
22. The method of Claim 20 wherein Y is a covalent bond or $-C(R_7R_8)-$ and R_7 and R_8 are each independently -H, an aliphatic or substituted aliphatic group, or R_7 is -H and R_8 is a substituted or unsubstituted aryl group, or, R_7 and R_8 , taken together, are a C2-C6 substituted or unsubstituted alkylene group.
23. The method of Claim 22 wherein the product compound is reacted with $Z-C(O)-Y-(CO)-Z$ and both Zs are -Cl or -OR, wherein R is phenyl or phenyl substituted with an electron withdrawing group.
- 15 24. The method of Claim 22 wherein the product compound is reacted with $HO-C(O)-CR_7R_8-C(O)-OH$ and a carboxylic acid activating reagent.
25. The method of Claim 24 wherein R_7 and R_8 are both -H.
26. The method of Claim 22 wherein R_1 is an aryl group or a substituted aryl group.

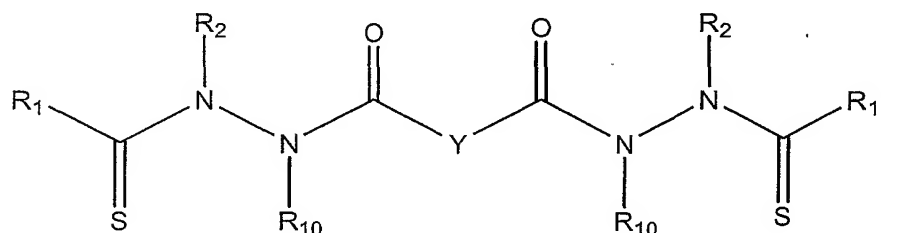
27. The method of Claim 26 wherein R_2 is an alkyl group or a substituted lower alkyl group.
28. The method of Claim 27 wherein R_2 is methyl or ethyl; R_7 is -H; and R_8 is -H or methyl.
- 5 29. The method of Claim 27 wherein R_1 is phenyl or substituted phenyl.
30. The method of Claim 29 wherein R_1 is phenyl and R_2 is methyl.
31. The method of Claim 29 wherein R_1 is phenyl substituted with one or more groups selected from -OH, -Br, -Cl, -I, -F, -OR^a, -O-COR^a, -COR^a, -CN, -NO₂, -COOH, -SO₃H, -NH₂, -NHR^a, -N(R^aR^b), -COOR^a, -CHO, -CONH₂, -CONHR^a, -CON(R^aR^b), -NHCOR^a, -NRCOR^a, -NHCONH₂, -NHCONR^aH, -NHCON(R^aR^b), -NR^cCONH₂, -NR^cCONR^aH, -NR^cCON(R^aR^b), -C(=NH)-NH₂, -C(=NH)-NHR^a, -C(=NH)-N(R^aR^b), -C(=NR^c)-NH₂, -C(=NR^c)-NHR^a, -C(=NR^c)-N(R^aR^b), -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR^a, -NH-C(=NH)-N(R^aR^b), -NH-C(=NR^c)-NH₂, -NH-C(=NR^c)-NHR^a, -NH-C(=NR^c)-N(R^aR^b), -NR^dH-C(=NH)-NH₂, -NR^d-C(=NH)-NHR^a, -NR^d-C(=NH)-N(R^aR^b), -NR^d-C(=NR^c)-NH₂, -NR^d-C(=NR^c)-NHR^a, -NR^d-C(=NR^c)-N(R^aR^b), -NHNH₂, -NHNHR^a, -NHN(R^aR^b), -SO₂NH₂, -SO₂NHR^a, -SO₂NR^aR^b, -CH=CHR^a, -CH=CR^aR^b, -CR^c=CR^aR^b, -CR^c=CHR^a, -CR^c=CR^aR^b, -CCR^a, -SH, -SR^a, -S(O)R^a, -S(O)₂R^a, alkyl groups, substituted alkyl group, non-aromatic heterocyclic group, substituted non-aromatic heterocyclic group, benzyl group, substituted benzyl group, aryl group or substituted aryl group wherein R^a-R^d each independently an alkyl group, substituted alkyl group, benzyl, substituted benzyl, aromatic or substituted aromatic group, or, -NR^aR^d, taken together, can also form a substituted or unsubstituted non-aromatic heterocyclic group.
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- 25 32. The method of Claim 26 wherein R_2 is a phenyl group or a substituted phenyl group.

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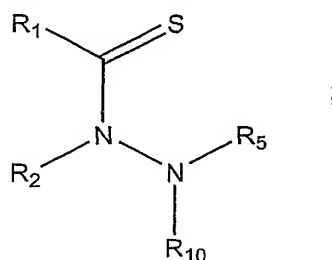
33. The method of Claim 22 wherein R_1 is an aliphatic group or a substituted aliphatic group.
34. The method of Claim 33 wherein R_2 is a phenyl group or a substituted phenyl group.
- 5 35. The method of Claim 34 wherein R_1 is a lower alkyl group and R_2 is a phenyl group substituted with one or more groups selected from -OH, -Br, -Cl, -I, -F, -OR^a, -O-COR^a, -COR^a, -CN, -NO₂, -COOH, -SO₃H, -NH₂, -NHR^a, -N(R^aR^b), -COOR^a, -CHO, -CONH₂, -CONHR^a, -CON(R^aR^b), -NHCOR^a, -NRCOR^a, -NHCONH₂, -NHCONR^aH, -NHCON(R^aR^b), -NR^cCONH₂, -NR^cCONR^aH, -NR^cCON(R^aR^b), -C(=NH)-NH₂, -C(=NH)-NHR^a, -C(=NH)-N(R^aR^b), -C(=NR^c)-NH₂, -C(=NR^c)-NHR^a, -C(=NR^c)-N(R^aR^b), -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR^a, -NH-C(=NH)-N(R^aR^b), -NH-C(=NR^c)-NH₂, -NH-C(=NR^c)-NHR^a, -NH-C(=NR^c)-N(R^aR^b), -NR^dH-C(=NH)-NH₂, -NR^d-C(=NH)-NHR^a, -NR^d-C(=NH)-N(R^aR^b), -NR^d-C(=NR^c)-NH₂, -NR^d-C(=NR^c)-NHR^a, -NR^d-C(=NR^c)-N(R^aR^b), -NHNH₂, -NHNHR^a, -NHN(R^aR^b), -SO₂NH₂, -SO₂NHR^a, -SO₂NR^aR^b, -CH=CHR^a, -CH=CR^aR^b, -CR^c=CR^aR^b, -CR^c=CHR^a, -CR^c=CR^aR^b, -CCR^a, -SH, -SR^a, -S(O)R^a, -S(O)₂R^a, alkyl groups, substituted alkyl group, non-aromatic heterocyclic group, substituted non-aromatic heterocyclic group, benzyl group, substituted benzyl group, aryl group or substituted aryl group wherein R^a-R^d each are independently an alkyl group, substituted alkyl group, benzyl, substituted benzyl, aromatic or substituted aromatic group, or, -NR^aR^d, taken together, can also form a substituted or unsubstituted non-aromatic heterocyclic group.
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- 25 36. The method of Claim 22 wherein R_2 is an aliphatic group or a substituted aliphatic group.

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37. The method of Claim 36 wherein R_1 is a lower alkyl group or a substituted lower alkyl group.
38. The method of Claim 22 wherein R_2 is an aryl group or a substituted aryl group.
39. The method of Claim 38 wherein R_2 is a phenyl group or a substituted phenyl group.
40. A method of preparing a product represented by the following structural formula:



said method comprising the step of reacting $Z-C(O)-Y-(CO)-Z$ or $HO-C(O)-Y-(CO)-OH$ and a carboxylic acid activating group with a thiohydrazide compound represented by the following structural formula:



wherein:

R_1 and R_2 are independently an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group, or R_1 and R_2 taken together with

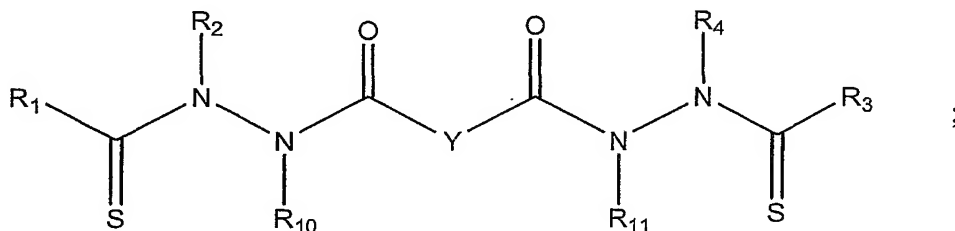
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the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_{10} is -H or an alkyl or unsubstituted alkyl group;

5 Y is a covalent bond or a substituted or unsubstituted straight-chained hydrocarbyl group; and
each Z is a leaving group.

41. A method of preparing a compound represented by the following structural formula:



10 wherein:

R_1 - R_4 are independently an aliphatic group, a substituted aliphatic group, an aryl group or a substituted aryl group, or R_1 and R_2 and/or R_3 and R_4 , taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

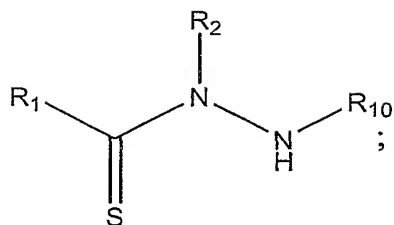
15 R_{10} - R_{11} are independently -H or a substituted or unsubstituted alkyl group;

Y is a covalent bond or a substituted or unsubstituted straight-chained hydrocarbyl group;

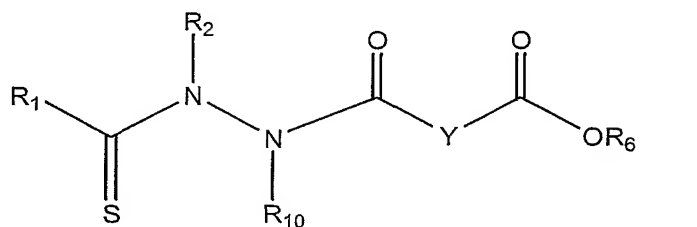
said method comprising the steps of:

a) reacting a first starting compound with $Z-(O)C-Y-COOR_6$ or with
20 $HO-(O)C-Y-COOR_6$ and a carboxylic acid activating group, wherein R_6 is a carboxylic acid protecting group, Z is a leaving group and the first starting compound is represented by the following structural formula:

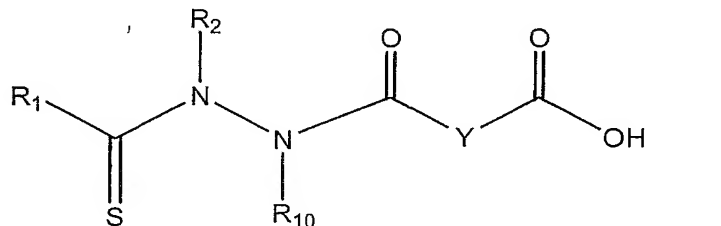
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thereby forming a first intermediate represented by the following structural formula:

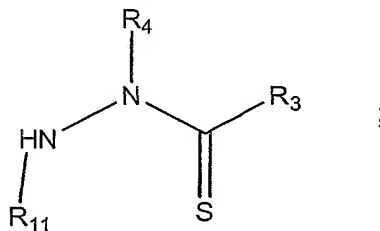


- 5 b) deprotecting the protected carboxylic acid group to form a second intermediate represented by the following structural formula:



- c) amidating the second intermediate with a second starting compound represented by the following structural formula:

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thereby forming the compound.

42. The method of Claim 41 wherein Y is a covalent bond, $-(CH_2CH_2)-$, *trans*-(CH=CH)-, *cis*-(CH=CH)-, $-(CC)-$ or a 1,4-phenylene group.
43. The method of Claim 41 wherein Y is a covalent bond or $-(CR_7R_8)-$ and R_7 and R_8 are each independently -H, an aliphatic or substituted aliphatic group, or R_7 is -H and R_8 is a substituted or unsubstituted aryl group, or, R_7 and R_8 , taken together, are a C2-C6 substituted or unsubstituted alkylene group and R_{10} and R_{11} are -H or an unsubstituted alkyl group.
44. The method of Claim 43 wherein the first starting compound is reacted in step a) with $Z-(O)C-Y-COOR_6$, wherein Z in step a) is -Cl or -OR and R is phenyl or phenyl substituted with an electron withdrawing group.
45. The method of Claim 43 wherein the first starting compound is reacted in step a) with $HO-(O)C-Y-COOR_6$ and a carboxylic acid activating agent and wherein the second starting compound is reacted in step c) with the second intermediate and a carboxylic acid activating agent.
46. The method of Claim 45 wherein R_7 and R_8 are both -H.
47. The method of Claim 41 wherein the carboxylic acid activating agent in step a) and step c) is dicyclohexylcarbodiimide (DCC).
48. The compound of Claim 43 wherein R_1 and R_3 are different and/or R_2 and R_4 are different.
49. The compound of Claim 43 R_1 and R_3 are different and R_2 and R_4 are the same.
50. The compound of Claim 43 R_1 and R_3 are same and R_2 and R_4 are different.

51. The compound of Claim 43 R_1 and R_3 are different and R_2 and R_4 are different.
52. The method of Claim 48 wherein R_1 and R_3 are independently an aryl group or a substituted aryl group.
53. The method of Claim 52 wherein R_2 and R_4 are independently is an alkyl group or
5 a substituted lower alkyl group.
54. The method of Claim 52 wherein R_2 and R_4 are independently a phenyl group or a substituted phenyl group.
55. The method of Claim 48 wherein R_1 and R_3 are independently an aliphatic group or a substituted aliphatic group.
- 10 56. The method of Claim 55 wherein R_2 and R_4 are independently a phenyl group or a substituted phenyl group.
57. The method of Claim 48 wherein R_2 and R_4 are independently an aliphatic group or a substituted aliphatic group.
58. The method of Claim 48 wherein R_1 and R_3 are independently an alkyl group or a
15 substituted alkyl group.
59. The method of Claim 48 wherein R_2 and R_4 are independently an aryl group or a substituted aryl group.
60. The method of Claim 48 wherein R_6 is a *tert*-butyl group.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C327/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CH 482 394 A (SHELL INT RESEARCH) 15 December 1969 (1969-12-15) column 5; example 1 column 7-8; table	1-39
X	TSUJI, T. ET AL.: "Synthesis and reactions of N-aminothiouracils and thiadiazolo[3,2- α]pyrimidinones" CHEM. PHARM. BULL., vol. 26, no. 9, 1978, pages 2765-2767, XP001118057 page 2765 page 2766, line 1,2 page 2767, line 21-25 -/-	1,2



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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- *A* document defining the general state of the art which is not considered to be of particular relevance
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International Application No
PCT/US 02/21716

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No:
X	PRZHEVAL'SKII, N.M. ET AL.: "A new general synthesis of bistetrafluoroborates of 2,3,4,5-tetrasubstituted 1,3,4-thiadiazoliums" SYNTHESIS, vol. 5, 1993, pages 463-464, XP00118228	1-3
Y	page 463, Scheme 1, 3 page 464, column 1, paragraph 1; table 1	1-39
X	BADAWY, M.A.: "Synthesis and reactions of 1,2,4-triazino-1,2,4-triazines" SULFUR LETTERS, vol. 11, no. 1-2, 1990, pages 21-28, XP00118568 page 24, line 1,2 page 26, line 9-12	1-3
X	MOHAMED M M ET AL: "SYNTHESIS & SOME REACTIONS OF 2-(ALPHA/BETA-NAPHTHYL)-3,1-BENZOXAZIN-4(H)-ONES. 3-AMINO-2-(BETA-NAPHTHYL)QUINAZOLIN-4(3H)-ONE" INDIAN JOURNAL OF CHEMISTRY, JODHPUR, IN, vol. 25B, no. 2, February 1986 (1986-02), pages 207-211, XP002914312 page 209, Scheme 3 page 211, line 18-23	1,2
X	BARTA-SZALAI, G. ET AL.: "Electron-deficient heteroaromatic ammonioamidates. XVII. N-(3-quinazolino)amidates. VI. The photochemistry of N-(3-quinazolino)amidates in the presence of alpha-toluenethiol" ACTA CHEM. SCAND. SER. B, vol. 33, 1979, pages 79-85, XP001107282 page 80, formulae 16, 17 page 82, column 2, line 21-24	1,2
X	UEDA ET AL.: NIPPON KAGAKU ZASSHI, vol. 80, 1959, pages 571-574, XP001118541	40
Y	page 572; table	20-60

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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	BRANCH, C.L. ET AL.: "Synthesis of 6-hydroxy-2-methyl-3-thioxo-2H-1,2,4-triaz in-5-one" SYNTHETIC COMMUNICATIONS, vol. 26, no. 11, 1996, pages 2075-2084, XP001118060 page 2077 page 2081, paragraph 3 -----	41-60

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Information on patent family members

International Application No

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